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THE BULLETIN OF Mathematical BIOPHYSICS

SEPTEMBER 1948

THE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS

VOLUME 10 · · · · · NUMBER 3

THE BULLETIN OF MATHEMATICAL BIOPHYSICS

EDITED BY N. RASHEVSKY

The Bulletin is devoted to publications of research in Mathematical Biophysics, as described on the inside back cover.

THE BULLETIN is published by the University of Chicago at the University of Chicago Press, 5750 Ellis Avenue, Chicago, Illinois, quarterly, in March, June, September, December. ¶The subscription price is $4.00 per year, the price of single copies is $1.25. Orders for service of less than a full year will be charged at the single-copy rate. ¶Patrons are requested to make all remittances payable to The University of Chicago Press in postal or express money orders or bank drafts.

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BUSINESS CORRESPONDENCE should be addressed to The University of Chicago Press, Chicago, Ill.

COMMUNICATIONS FOR THE EDITOR and manuscripts should be addressed to N. Rashevsky, Editorial Office of the Bulletin of Mathematical Biophysics, 5822 Drexel Avenue, Chicago, Ill.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 10, 1948

PHYSICAL ASPECTS OF ORGANIC EVOLUTION*

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The system composed of species of living organisms and their environment evolves under a stream of available energy from the sun. The differential survival of the components depends on the degree of success of each in securing its share of energy from this stream.

This type of problem is familiar from the study of physicochemical systems in which the distribution and change in distribution of matter among specified components is examined in its relation to parameters of state. But whereas it is characteristic of physicochemical systems commonly considered that structure and mechanism play at most a subordinate role, in the study of organic evolution the structure and mechanical properties of the components, on which their aptitude for capturing energy depends, play the dominant role.

If we ask ourselves what we mean by the evolution of a material system, I think you will agree with me, upon reflection, that we mean its history, the succession of past and future states through which it passes. We further have in mind that particular type or kind of history which bears a distinctive stamp of a forward direction in time, as distinguished from a strictly periodic sequence which repeats the same cycle over and over, or a purely changeful sequence in which no characteristic difference between forward and backward direction in time is discernible. Just what fundamentally distinguishes the forward direction in time we shall not on this occasion seek to discuss nor, indeed, can there be any question here of discussing in its entire generality the evolution defined as above. We are interested for the moment in a particular kind of system, and in certain particular aspects of the evolution of a system of this kind.

The aspect of evolution with which we are here concerned is

* Address delivered before the Symposium on Mathematical Biology held during the meeting of the A.A.A.S. in Chicago, December 26–27, 1947.

Other papers presented at the Symposium are also being published in *The Bulletin*. Those include:

Rapoport, Anatol and Shimbel, Alfonso. 9, 169, 1947; Culbertson, J. T. 10, 31, 1948; Rapoport, Anatol and Shimbel, Alfonso. 10, 41, 1948; Hearon, John Z. 10, 175, 1948; Morales, Manuel F. and Smith, Robert E. 10, 191, 1948.

For technical reasons the papers are not published in the same order as they were presented. A complete list of the papers presented at the Symposium on Mathematical Biology, together with abstracts is published in *Biometrics*, 4, No. 2, 1948. EDITOR.

that which views the system under consideration as built up of certain components, and which contemplates the distribution and the changes in the distribution of the substance of the system among these components.

The particular aspect of the problem regarding such systems which we choose to study evidently depends on the manner in which the components are defined or described. We may be concerned with the course of events in a system composed of stated chemical elements or compounds, or phases of such, which are capable of physicochemical interaction. We may then ask what changes will take place in the composition so defined, of the system, and, in particular, we may ask, do these changes tend in some particular direction or toward some particular ultimate state? We may also ask, how is the direction of these changes and the end state characterized? As you know, the course of such physicochemical evolution is such that under certain conditions a function *of the system as a whole,* its thermodynamic potential, tends toward a minimum.

But we who are meeting here today, a sort of crossbreed between physicists and biologists, have a special interest in the evolution of a system somewhat differently defined. The system before our mind's eye is not contained in a test tube or flask in the laboratory. It is spread as a relatively thin film—the biosphere—over or near the surface of our globe. Its components, as regarded from our point of view, are biological species, themselves subdivided into individual organisms.

What interests us here is the distribution, and changes in distribution, of the total substance of this system among its several component species; and, in further detail, the changes in the frequency distribution, within each species, of varieties of individuals comprised therein. A mental construct, a geometric representation, is perhaps helpful here in vividly portraying the nature of the processes to our mind. If we imagine the character of each individual organism as represented by a point in n-dimensional space, corresponding to the values of n characteristics in terms of which the organism is defined or described, then we would see the state of the entire system at any particular moment represented by a number of separate clusters or clouds of points, each cloud corresponding to one species. Each such cloud would exhibit a varying density of points within its boundary. With the passage of time we should observe two kinds of changes. The masses of the several clouds would change—in accordance with the process of inter-species evolution; and, within each cloud, the distribution of point densities would change. Changes of this latter kind, intra-species changes would, in general, affect the boundaries of the

individual clouds; so much so, in some cases, that after a sufficient lapse of time the new position of the cloud would lie entirely outside of its original position, thereby representing what would be regarded as a new species.

Changes of the second kind—intra-species evolution—obviously have a certain special interest and there has been a tendency to concentrate on this aspect of evolution. On the present occasion, I propose to concentrate our attention rather on the first kind of changes, the inter-species evolution of the system, that is, the changes in the distribution of the matter of the system among the several component species. These changes are often relatively rapid, so that in contemplating them we may in first approximation often disregard the slow changes of intra-species evolution.

In approaching the problem of the physics of organic evolution, we have the advantage of being able to profit from our experience with the somewhat simpler and more completely worked out problem of physicochemical evolution. Let us consider some of the points of similarity and some of the points of difference between the two problems.

That they are of the same general type follows directly from the way in which we have defined evolution—as a change in the distribution of matter. But to one point of similarity I wish to draw particular attention. The evolution considered in each case is the evolution of the system as a whole. In the reaction

$$2H_2 + 0_2 \rightleftarrows 2H_20$$

we are not discussing the history of the hydrogen in the system, or of the oxygen, but the history of the system as a whole. In seeking the fundamental principles of organic evolution we may be assured that we shall make adequate progress only by considering a system of coexisting organisms and their environment as a whole. For example, it is fruitless to ask whether the trend of evolution is toward low mortality accompanied by low fertility or, on the contrary, toward high fertility counterbalancing high mortality. The fact is that organisms of both these extreme types have been evolved, forming in many cases a system of interdependent prey and predator species. If we seek a basic law of evolution, we may be assured that it will be formulated in terms of a system of interdependent species and their environment *as a whole.*

But while we shall no doubt be well advised to give an important place in our thoughts to these points of similarity, there are certain points of difference of equal importance.

1. In the discussion of physicochemical systems, chemical com-

position plays a dominant role, and structural features at most play only a secondary role—often no explicit role at all.

In the case of the system of organic nature, this situation is reversed. A sheep may not differ very greatly in chemical composition from a lion; what sets the two apart and determines their relative roles in the scheme of nature is their widely different *structure* and corresponding behavior pattern.

Whereas the possible physicochemical transformations in a given system are limited, possible changes in structure are, in principle, unlimited. In accordance with this, the evolution of a physicochemical system under stated conditions is commonly a process which terminates.* Organic evolution, on the other hand, because of the infinite possibilities of changing structure, is apparently a continuing process without an end *under given conditions.*

2. Much of the theoretical discussion of physicochemical evolution relates to systems proceeding toward an equilibrium in which the system is self contained, in the sense that it receives no energy from outside.

Organic evolution on the earth, on the other hand, is typically a process taking place under a continuous stream of energy from an outside source, the sun.† Wherever our investigation of the physics of organic evolution may lead us, of this we can be sure— no treatment of the problem which fails to give a prominent place to this feature can really strike at the root of the matter. Our fundamental purpose must be not merely to formulate the law of organic evolution as an empirical fact—whether in terms of "increasing organization" as some have proposed, or in any other terms—but to deduce this law, whatever its form, as a necessary consequence of fundamental physical principles.

Certainly, the discovery of empirical relations is not without interest, but it must be kept in mind that such relations pose a problem rather than solve one. When we observe an empirical law we ask, why this law, if such it be?

3. A third distinctive characteristic of organic evolution as against physicochemical evolution is this:

In the study of physicochemical systems, the bulk properties of the components are readily accessible to observation and form the first point of attack. The investigation of the properties of the finer units, molecules, atoms, etc., on the contrary, requires special highly refined methods.

*Theoretically this may require an infinite time, but in practice the end state is commonly attained within close limits in a finite time.

† In this respect it resembles photochemical reactions.

In studying the system of nature in the course of organic evolution, this situation is essentially reversed. The individual units, the individual organisms, being in many cases of dimensions comparable with our own, are commonly quite easily accessible to direct observation. It is rather the collective or bulk properties of populations of organisms that more severely tax our resources for investigation by field studies, statistical methods, etc.

Since there are these two avenues of approach available in the study of an evolving organic system, we may profitably proceed along both. It is to be noted, however, that the second method, based on the observation of bulk phenomena, tends in the first instance to lead to empirical generalizations, the inner significance of which is often not apparent, but needs to be peeled out from the empirical context by a separate investigation. The fact is that these bulk or collective phenomena are not really and fully understood until their relation to the properties of the individual organisms and the environment in which they play their part is clearly laid bare. In this respect the first method, which proceeds outward from a study of the individual organisms to a comprehension of their collective effects, promises to be the more efficient, the more directly productive of fundamental results.

With these significant points of similarity, but also no less important points of distinction between the two cases of evolution—physicochemical and organic—we may indeed draw profit from the experience gained in the study of the first case, but on the condition that we proceed guardedly. That this caution is necessary is evident from instances on record of undue significance attached to surface analogies. For example, the principle of Le Chatelier has been stated in the form: "Every external action produces in a body or system a change in such direction, that in consequence of this change the resistance of the body or the system against the external action is increased." (Chwolson, 1905, p. 475.)

Even as applied to a chemical transformation the statement in this form can be misleading, since it does not clearly indicate what is meant by "resistance." The fallacy arises from the fact that this form of statement fails to distinguish between the intensity and the capacity factor of the energy involved.

Still less is the principle in such vague form capable of useful application to systems composed of or comprising living organisms, as has been repeatedly suggested (Chwolson, 1905, p. 476; Bancroft, 1911, p. 92) without even indicating what particular parameters are referred to by such terms as "external action," "direction," "resistance."

Again, V. Volterra (1937)* in his mathematical analysis of the interaction of coexisting organic species introduces such concepts as *action vitale élémentaire, travail virtuel d' accroissement, énergie démographique actuelle et potentielle,* etc., which are so termed quite frankly by *analogy* to certain quantities or entities rigorously defined in physics.† The impression is thus given that Volterra's analysis is an application of rigorous physical principles to biology. Actually, of "energy" or "action," in the strict sense in which the physicist uses these terms, there is no mention or even definite implication in Volterra's analysis. There is danger that by hastily giving to certain mathematical constructs the names of established physical entities, we desist from further efforts to fathom the truly physical relations involved.‡

If now we turn from verbal imitations of physical concepts to view our problem of organic evolution in its truly physical aspects, what is the general outlook that presents itself to us?

We contemplate an aggregation of energy transformers of distinctive structure and function, the living organisms. A characteristic of such an organism is that it maintains its state of being by the expenditure of certain quantities of substance and energy, which its distinctive structure enables it to recoup from external sources.

These sources are, broadly classified, of two kinds: The first kind are distributed in space in essentially continuous fashion—matter in the form of gases (CO_2, N_2), and substances dissolved or capable of being somewhat readily dissolved; and energy, in the form of radiant energy pouring down upon the earth from the sun.

The second kind of sources are distributed in essentially discontinuous fashion, matter and energy of plants and animals upon which the organism feeds, thus deriving at one time both substance and energy needed for its maintenance and growth.

*He himself puts it this way: "On peut appeller action vitale élémentaire (une certaine expression analytique) *en voulant adopter une locution analogue* à celle qu'on emploie en mécanique."

†Actually these physical prototypes and their analogues in Volterra's analysis are of totally different dimensions, a fact which he passes over in silence.

‡This reflection should make it evident that I am not here offering a mere verbal quibble. A quotation is apposite. In a paper, *The Place of Geophysics in a Department of Geology* M. King Hubbert (1938) remarks: "A common error arises when the workers in one field, impressed by the successes of workers in another have set about to find an *analogy* between the phenomena of the two fields, so that analogous relations could be established; or, as sometimes happens, when the successful worker in a certain field attempts to solve the problems in another by an incorrect analogy."

One of the most extensively "borrowed" physical terms is that of "potential." As Volterra (1937) speaks of *potentiel démographique,* so L. Hersch (1940) of a *potentiel-vie*; P. Vincent (1945) of *potentiel d'accroissement*; J. Q. Stewart (1947) of "potential of population"; L. C. Birch (1945) of a biotic potential. None of the quantities referred to in these terms is of the dimensions of a physical potential, that is, energy in the strict physical sense.

Corresponding to these two types of sources of matter and energy are two broad classes of organisms: Green plants, characteristically, though not universally, sessile, since they can sit and wait for food to come to them. And animals, characteristically, though not universally, mobile, since for the most part they have to go foraging for their sustenance. Because of this mobility, and the "ingenious"* mechanism with which they are provided for carrying on their life—sustaining activities, these organisms, the more highly developed animals in particular, present features of the greatest interest, and I propose in what follows to concentrate our reflections on this type.

In seeking to approach a problem by the methods which modern science has developed with such success, it may not be amiss to make some observations in passing regarding one of the characteristics of the scientific method, to which undoubtedly much of its success is to be credited. The history of science itself gives us a clue. Among the earliest branches of science to be developed with very creditable results was astronomy. This science profited by the advantage that its data came in about the simplest possible form: mathematical points.† Without further elaboration of its raw material the science could proceed to observation and to systematization of its findings.

As an example at the opposite extreme one might perhaps cite chemistry, one of the latest sciences to be developed. It could not progress to any significant stage until out of the hodgepodge of matter in nature, elements and compounds had obtained separate recognition and understanding.

The science of physics may be said to have occupied, historically, a position between these two extremes. The physicist has his own way of securing that relative simplicity of basic data which is necessary for the fundamental attack on scientific problems: He can mold his material to size and shape—a cube of given side, a wire of given gauge and length, etc.

He has also another expedient which has proved of inestimable value as a tool for the discovery of fundamental principles, a method which in a language just now somewhat unpopular, but rather well adapted for coining words, has been termed the *Gedankenexperiment.* I well recall how, in my verdant undergraduate days, I was half amused at the "naive" engine by the aid of which Carnot's cycle and thence the second law of thermodynamics was developed *on the blackboard,* if you please . Here was an engine consisting of a cylinder with perfectly insulating sides and a perfectly conducting bot-

*I have tried unsuccessfully to find a word without anthropomorphic flavor to describe the quality in question.

†To the naked eye and the simple instruments of early astronomers planets as well as stars were practically points.

tom. A source with similarly fantastic qualities completed the installation. No such engine ever existed except on the blackboard, none such in "real life." I took occasion after the lecture to remark to Poynting about it. "Yes," he replied, "but you will see what far-reaching consequences follow."

With these lessons from the history of science before us, what shall we do with our problem of the dynamics of an aggregate of interacting energy transformers possessed of the characteristics of living organisms?

We cannot make our organisms over to measure and scale. But in imagination we can mold them at pleasure as to their fundamental physical characteristics. I suggest that we try the method of abstraction which has been so fruitful elsewhere. If some of our premises appear "naive," and perhaps tempt a smile to some lips, let us not be discouraged at the start.

We begin on familiar ground. To get down to essentials we dissect the organism—not in the laboratory with scalpel and forceps, but with our analytical faculties. In the working of the animal energy transformer we distinguish certain fundamental parts or elements.

(a) *Receptors,* which *depict* features of the environment in the organism. The typical example is the eye; but more generally, sense organs fulfil this function. Their efficiency is, in principle, susceptible of numerical measure, as for instance visual acuity, or range of visibility for an object of given size.

(b) *Elaborators,* which derive from the raw material supplied by the receptors, secondary information supplementing the picture of the environment as depicted by the receptors. These elaborators are developed to an outstanding degree in man, where they include the "logical" faculties. I have at the moment no suggestion to make for the numerical treatment of the elaborators. Except in man they play a subordinate role and may perhaps in first approximation be left out of account.

(c) *Effectors,* by which the organism reacts upon the environment, whether it be by its own locomotion to change its position relative to features in the environment, or by modifying the environment itself.

The effectors operate with an expenditure of free energy released by *trigger action,* a fund of such free energy being present as a characteristic endowment of every living organism. One of the functions of the effectors is to gather or capture free energy and material substance from available sources, to recoup that expended or "lost" in their activity. Losses of entire organisms must be made good by the growth (birth, etc.) of new organisms, which is provided for in

the normal cycle of existence of the organism.

Another function of the effectors is to perform acts of defense against or escape from situations harmful or fatal to the continuous existence of the living organism. Failure to escape, which for many species is an unavoidable risk, constitutes one of the sources of the losses referred to in the preceding paragraph.

Escape from hazard commonly takes place by flight to a refuge, such refuges* being scattered over the topography in which the organism operates (Lotka, 1928, 1932; Elton, 1939).

A numerical measure of the efficiency of the effectors will in many cases suggest itself, such as for example the maximum velocity in pursuit or escape; the relative "strength" available, as measured in first approximations by size;† the passive resistance to crushing (as in the shell of a tortoise); etc. (Elton, 1927.)

As to the energy relations involved in the operation of the effectors, account must be taken, not only of the energy expended in the essential activities (pursuit, flight, etc.), but also in what might be termed incidentals. These would include seemingly aimless "random migration" and play activities, as well as the physiological work that continues quite aside from any outward activity. In a sense the organism may be likened to an automobile whose motor cannot be stopped, so that it goes on "idling" even when the car is standing still.

(d) *Adjustors,* which determine what action the effectors shall perform, in accordance with the information (picture of the environment) supplied by the receptor, as supplemented by the elaborators.

The quantitative treatment of the adjustors requires a special approach; for, their function is to determine the *choice* between various forms of energy expenditure by the organism, among the several opportunities open to it. If the organism can operate to modify various parameters Q_1, Q_2, $\cdots$, by increments ∂Q_1, ∂Q_2, $\cdots$, and if each such increment separately brings with it an increase ∂r in the rate of increase r per head (or per unit of mass) of the species then, from the point of view of purely material advantage to the species,‡ the ideal adjustment would be that which would make r a maximum.

*A refuge is any part of the topography rendering the prey organism inaccessible to the predator; for birds, for example, the air or the branches of a tree, or a sheet of water in the case of aquatic species, present a refuge against most ground living animals.

†In this connection an interesting point to note is the observation that a food chain (each member functioning as prey to the preceding) usually does not greatly exceed five links.

‡The case of the human species, in this as in other respects, brings up special problems. We do not look upon mere multiplication of our species as a desideratum. The problem of *optimum* population, which arises here, will not form part of the present discussion.

From this ideal adjustment the several species will deviate in varying degree.

In the case of man, when the choice is made consciously, it is experienced as a judgment of the *value* of the different actions or of the things secured by these actions. Thus the economist's *value in exchange* (commonly measured in money) is seen to be related to an entity of the dimensions of $\frac{\partial r}{\partial Q}$, and we have here another instance of loose application of an analogy when certain writers* speak of *economic energy,* of which *value* is to be the intensity factor.

The physical characteristic of the adjustors is that they guide, through *trigger action,* the release into suitable channels of portions of the free energy at the disposal of a living organism. It is the action of the adjustors—whether in elementary form through reflex action, or in the form of *voluntary* action as developed to its highest degree in man—that imparts especially to the higher forms of organisms the quality of *Maxwell Demons* on a molar scale.†

Here we run into the phenomenon of *will,* which seems to be quite foreign to and outside the scope of contemporary physics. Certainly we shall not expect to find any reference to it in any of the current textbook of physics. Nevertheless, this phenomenon of *will* does have a certain definite physical context. Willed actions are possible only to structures disposing of a fund of free energy—structures which in that sense are in a metastable state. One cannot will a *past* event, *will* necessarily involves the *future,* just as the metastable state contains the seed of the future. We are not, then, wholly without a connecting link between physics and the phenomenon of *will.* A big question mark, of course, remains as to the significance and the role of consciousness in the operation of the organism,‡ but we shall not wait to see all questions resolved before proceeding in our reflections and investigations of the physical aspects of life and of the evolution of living organisms.

Having thus dissected the organism (more especially the animal

*Notably G. Helm, (1887).

†It should hardly be necessary to point out once again that this does not involve any infringement of the second law of thermodynamics, since we are not dealing with an isolated system, but with one that is currently receiving a stream of free energy from the sun.

‡I have elsewhere suggested that perhaps the intervention of consciousness for the performance of many tasks that can also be performed by non-living mechanisms may be nature's way of achieving an economy of parts. Certainly, to perform the well nigh infinite variety of tasks of which for example a human individual is capable, would require, at best, a gigantic installation. So we have become accustomed lately to calculating machinery that fills an entire room of considerable dimensions. Compare this with the compactness of the human brain.

type) down to fundamentals, that is, to those qualities and functions not peculiar to one particular organism or species, but characteristic of and possessed by a large and representative group of organisms—we are now prepared to proceed with our *Gedankenexperiment.*

You may, if you like, regard this as just a game. But let me remind you that the theory of probability, with all its modern highly technical applications, arose on the foundation of seemingly frivolous inquiries regarding games of chance.

Our game, then, will be of the type which, like chess, is played upon a "board," that is, a topographical map.

Since we are dealing with an abstraction we have considerable freedom in designing this map, so long as it conforms to the type of our problem—that is to say, it will contain scattered refuges. To start with something simple, we may suppose the refuges arranged according to some geometrical pattern, say hexagonally. Over this topography we may suppose, again for simplicity as a starting point, two species operating, a predator species and its prey. To each we can assign specific receptors, effectors and adjustors, choosing again, for a beginning, very simple specifications. The prey species, we may suppose, subsists upon some food present in abundance, so that its supply may for purposes of the example be regarded as essentially constant.

With this setting (to which we may perhaps find it necessary to add further data) we may investigate the conditions for capture, the frequency of capture, and the consequences for prey and predator species, both of the conditions as first assumed, and of any modifications in these conditions which we may further contemplate.

As I have elsewhere given indications of the kind of approach that may be made to this problem, I need not here repeat these suggestions. But this I should like to say: On the most conservative estimate, suppose we are merely playing a game. When we think of all the time and mental application that has been and will continue to be spent on playing chess, bridge, checkers and the like—to say nothing of books, some of them most profound, that have been written on these games and on the theory of games generally*—when we think of all the efforts thus spent, will not our game at least have the merit of being related to profound problems of real life, as against the relative trivialities of parlor diversions?

If our most modest expectations should be exceeded, if our *Gedankenexperiment* should yield even only a fraction of the results that have sprung from Carnot's ideal heat engine, we should be well

*Outstanding in this field is the recent brilliant work of von Neumann and Morgenstern (1944).

served.

Perhaps one result which we might expect is a rigorous confirmation of a maximum law, which I have elsewhere suggested as the law of organic evolution. If I may, somewhat inadequately, summarize in one sentence what I have expounded more at length elsewhere, (Lotka, 1945) it would be to this effect:

All in all, those species have the advantage which know best how to tap *and put to favorable use* the stream of energy available in nature. Collectively, this will tend to increase the flux of energy through the system of organic nature, which flux may thus be said to be approaching a maximum.

The function of the adjustors in "putting to favorable use" the energy captured has today risen to superlative importance, beyond all previous conception, by the tapping of that new and unparalleled source, nuclear energy.

In point of control over immense powers this new development has placed man, out of all proportion, above other living species. Whether he will profit by the new opportunity, and thus continue the process of increasing the energy flux through the system of organic nature, or whether his species will prove unfit by turning the new power against itself, this will be the supreme test of the adequacy of his adjustor faculties. If he fails in the test, evolution may have to make a fresh start from a lower level, either with some of the less advanced sections of the human race that may be saved from the holocaust, or with some other "inferior" species. Should this occur, it will be another example of a phenomenon not unfamiliar in paleontology, a species that has become the victim of overspecialization.

* * *

In addressing you here today I have admittedly presented to you a program rather than a report of results. For this I believe I need make no apology, since one of the main purposes of these meetings is to afford opportunity for interchange of ideas, and to stimulate thought.

In this I trust I have not altogether failed.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 10, 1948

THEORY OF THE MEASUREMENT OF BLOOD FLOW BY THE DILUTION OF AN INDICATOR

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It is shown that the instantaneous concentration of an indicator at one point in a circulation can be related to all previous concentrations at a second point by an integral equation. Solutions of this equation give formulae for the computation of the mean transit time, the flow, and the volume of the circulation between the two points.

Cardiac output has been estimated by injecting a salt or a dye into a vein and measuring its concentration in an artery (Stewart, 1897; Hamilton and Remington, 1947.) This paper presents a theory for the interpretation of such measurements.

It is useful to think of the movement of blood from the left heart as resembling a river which separates into several branches that flow into a like number of swamps, the systemic capillaries. Their drainage forms a single stream which again divides and runs through a second set of swamps, the pulmonary capillaries. However, the flow through the swamps differs from the sanguinous circulation—drainage from the second swamps is to the ocean, but from the pulmonary capillaries drainage is again to the left heart.

Suppose at the moment $t = 0$ we *suddenly* add to the inflow of the swamps an amount M of an indicator I, which stays in the stream. If $f(t)$ is the probability that it takes a particle the interval of time t to traverse the swamps, then the fraction of M flowing out of the swamps at time t will be $f(t)$ and hence the rate of drainage of I from the swamps will be $\frac{dM}{dt} = Mf(t)$ or

$$dM = Mf(t)\,dt\,. \tag{1}$$

If F is the flow through the swamps per unit time, the drainage from the swamps in the time dt is Fdt. Hence the cross-stream average concentration C of I is

$$C(t) = \frac{dM}{Fdt} = \frac{Mf(t)}{F}. \tag{2}$$

Equation (2) can be generalized so as to relate the concentration of I in the drainage, C_2, to the concentration in the inflow, C_1. The fraction of $C_2(t)$ contributed by the inflow at time, $t-\eta$, is

$$dC_2(t) = C_1(t-\eta) f(\eta)\, d\eta . \tag{3}$$

Integration over all previous time gives

$$C_2(t) = \int_0^\infty C_1(t-\eta) f(\eta)\, d\eta . \tag{4}$$

Equation (2) does not apply to circulations because it does not account for indicator fed back into the inflow from the drainage, e.g., indicator passing through the system for a second or third time. The quantity C_1 in equation (4) includes all I. Hence equation (4) should be used in calculating the behavior of a circulation.

It is easy to solve equation (4) when I is added to a circulation at a constant rate m. Conceive circulation from X to Y, from Y to Z, and from Z to X. Then Y, the point of addition, is "between" X and Z. The quantity C_1 at X is related to C_2 at Z by

$$C_2(t) = \frac{m\theta(t)}{F} + \int_0^t C(t-\eta) f(\eta)\, d\eta , \tag{5}$$

where $\theta(t)$, an arbitrary function accounting for transients, increases monotonically, $0 \leqq \theta(t) \leqq 1$.

The average concentration of indicator throughout the circulation at time t is mt/V, where V is the volume of the circulation. Since for capillary beds $f(t)$ is not a delta function* or a sum of delta functions, transients are damped and C at any point approaches $m(t-a)/V$, where a depends on the point of addition.

As $t \to \infty$,

$$C_2(t) \to \frac{m}{F} + \int_0^\infty \frac{m(t-a-\eta)}{V} f(\eta)\, d\eta \tag{6}$$

or

$$C_2(t) = m/F + C_1(t) - mb/V, \tag{7}$$

*A "delta" function is an impulse function which is defined in the following way:

$$\delta(t-t_0) = \lim_{a\to 0} \frac{1}{\sqrt{2\pi}} \frac{e^{-\frac{(t-t_0)^2}{2a^2}}}{a}$$

$$\int_{-\infty}^{\infty} \delta(t-t_0)\, dt = 1 .$$

where b is the average time of transit from X to Z. If the point of injection is "between" Z and X,

$$C_2(t) = C_1(t) - mb/V. \tag{8}$$

Equations (7) and (8) give the flow through and the volume of any part of a circulation. Thus, let I be injected into the right heart at the rate m. The concentration in the aorta is

$$C_{a_1} = C_{v_1} - mb/V + m/F, \tag{9}$$

where F is the cardiac output, b is the mean transit time from the right heart to the aorta, V is the blood volume, and C_v is the concentration of I in the superior and inferior venae cavae.

Let I be injected into an arm or leg vein; then

$$C_{a_2} = C_{v_2} - mb/V. \tag{10}$$

Equations (9) and (10) determine b and F for known V, which can be easily found from the final dilution of a known amount of a blood volume dye. The volume of the pulmonary circulation is

$$V_p = Fb. \tag{11}$$

Our interpretation of F will depend on our anatomical knowledge. Thus, if C_1 is for the internal carotid artery and C_2 is for the internal jugular vein, F is the flow through the internal carotid plus other inflow to the circle of Willis.

Since injection at a constant rate may not be experimentally feasible, more general methods of computation are necessary. These methods depend upon determining $f(t)$, which may be found from equation (4).

If for $t < 0$, $C_1(t) = 0$, equation (4) becomes

$$C_2(t) = \int_0^t C_1(t-\eta) f(\eta)\, d\eta. \tag{12}$$

Differentiation gives

$$C_2'(t) = C_1(0)\, f(t) + \int_0^t C_1'(t-\eta) f(\eta)\, d\eta. \tag{13}$$

Solving for $f(t)$, we have

$$f(t) = \frac{C_2'(t)}{C_1(0)} - \frac{1}{C_1(0)} \int_0^t C_1'(t-\eta) f(\eta)\, d\eta. \tag{14}$$

Successive substitution of the expression for $f(t)$ given by the right-hand side of equation (14) in $f(\eta)$, which occurs on the right-hand side, leads to a formal solution, namely, the series:

$$f(t) = \frac{C_2'(t)}{C_1(0)} - \frac{1}{C_1(0)} \int_0^t C_1'(t-\eta_1) C_2'(\eta_1)\, d\eta_1$$
$$- \sum_{m=2}^{m=\infty} \left(- \frac{1}{C_1(0)} \right)^{m+1} \int_0^t C_1'(t-\eta_1) \int_0^{\eta_1} C_1'(\eta_1 - \eta_2) \qquad (15)$$
$$\cdots \int_0^{\eta_{m-1}} C_1'(\eta_{m-1} - \eta_m) C_2'(\eta_m)\, d\eta_m \cdots d\eta_1 .$$

This series converges for all finite values of t, because $|C_1'(t)| \leqq P$ and $|C_2'(t)| \leqq Q$, where P and Q are positive numbers. Hence,

$$f(t) \leqq \frac{Q}{C_1(0)} \left[1 + \frac{Pt}{C_1(0)} \cdots \frac{1}{n!} \left(\frac{Pt}{C_1(0)} \right)^n + \cdots \right], \qquad (16)$$

or

$$f(t) \leqq \frac{Q}{C_1(0)} e^{\frac{Pt}{C_1(0)}}.$$

As $t \to \infty$, a sufficient condition for convergence is that $|C_2'(t)| \leqq Q$ and that

$$\int_0^\infty |C_1'(t)|\, dt \leqq C_1(0).$$

If $C_1(0) = 0$, equation (15) has no meaning. In that case, differentiation of equation (13) gives

$$C_2''(t) = C_1'(0) f(t) + \int_0^t C_1''(t-\eta) f(\eta)\, d\eta . \qquad (17)$$

If $|C_1'(0)| > 0$, this equation can be solved for $f(t)$ as above. The proof of convergence is similar.

A more elegant method of solution of equation (14) is by Laplace transforms (Churchill, 1944). It can be written as the general integral equation of the convolution type,

$$Y(t) = F(t) + \int_0^t G(t-\eta) Y(\eta)\, d\eta , \qquad (18)$$

whose transform is

$$y(s) = f(s) + g(s) y(s) \qquad (19)$$

or,

$$y(s) = \frac{f(s)}{1 - g(s)}. \qquad (20)$$

The inverse of equation (20) gives $Y(t)$, which corresponds to $f(t)$ of equation (14), as an explicit function.

Thus we obtain formulae for the computation of $f(t)$ which are independent of the method of injection, although concentrations following instantaneous injection should give a most rapidly convergent solution.

Once we know $f(t)$, we can easily correct concentration curves for recurrent indicator and find the mean transit time, flow, and volume for a part of the circulation. The only limitations of the method are the accuracy with which measurements of instantaneous concentration can be carried out and the degree to which circulation is altered as a result of experimental manipulation.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 10, 1948

INTERACTION OF CYCLES

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We discuss under the McCulloch and Pitts assumptions for neural nets a circuit consisting of k cycles such that one cycle is activated by an outside stimulus and sends an impulse to a second cycle which in its turn sends an impulse to the next cycle, etc., up to the kth cycle, which sends an impulse to a response. We thus have a "series" of k cycles "interacting." We give several theorems regarding the response patterns of such circuits under the additional constraint that the stimulus acts but once, and at the time it acts the circuit is at rest.

The circuits discussed here are of the McCulloch and Pitts (1943) microscopic type. The general representation of the kind we will consider is shown in Figure 1. It has k cycles which have

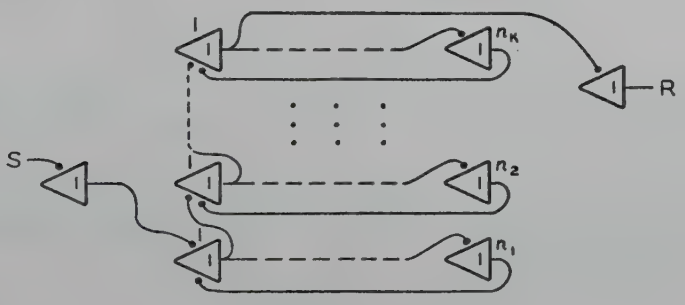

FIGURE 1

$n_1, \cdots, n_k$ synapses respectively. We define the class of all response times of R to be $\mathcal{R}_k$. We consider the members of $\mathcal{R}_k$ as pure numbers. In addition, we allow S to act but once and specify this action time to be $\tau_s = -(k+2)$, where k is again the number of cycles. With this value of τ_s we are always assured of having zero as the smallest member of $\mathcal{R}_k$.

For $k = 1$ we have for $\mathcal{R}_1$:

$$\mathcal{R}_1 = \{0, n_1, 2n_1, \cdots\}$$
$$= \{i_1 n_1\}; \quad (i = 0, 1, 2, \cdots).$$

Taking $k = 2$

$$\mathcal{R}_2 = \left\{ \begin{array}{l} 0\,,\, n_1\,,\, 2n_1\,,\, \cdots \\ n_2\,,\, n_1 + n_2\,,\, 2n_1 + n_2\,,\, \cdots \\ 2n_2\,,\, n_1 + 2n_2\,,\, 2n_1 + 2n_2\,,\, \cdots \\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot \\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot\ \cdot \end{array} \right\}$$

$$= \{i_1 n_1 + i_2 n_2\}; \qquad (i_{1,2} = 0\,,1\,,2\,,\cdots).$$

Continuing in this manner, we obtain the expression for $\mathcal{R}_k$ in terms of the numbers of synapses in the cycles.

$$\mathcal{R}_k = \{i_1 n_1 + \cdots + i_k n_k\}; \qquad (i_j = 0\,,1\,,2\,,\cdots). \tag{1}$$

In other words, $\mathcal{R}_k$ consists of all integers that are sums of non-negative multiples of the numbers $n_1\,,\cdots,\,n_k$. Our problem is to find out what integers are included in $\mathcal{R}_k$ for an arbitrary set $n_1\,,\cdots,\,n_k$ of numbers.

Theorem I. Given that:

1. $\mathcal{R}_k = \{i_1 n_1 + \cdots + i_k n_k\}; \qquad (i_j = 0\,,1\,,2\,,\cdots),$
2. $(n_1\,,\cdots,\,n_k) = 1\,,$ then;

$$(EN)\,(i)\,(N \varepsilon \mathcal{R}_k \cdot i \geqq 0 \rightarrow N + i\varepsilon\mathcal{R}_k). \tag{2}$$

This theorem states that if the *GCD* of $n_1\,,\cdots,\,n_k$ is one, then there exists an integer N in $\mathcal{R}_k$ such that every integer greater than N is also in $\mathcal{R}_k$.

Proof: We know from number theory that if the *GCD* of k numbers $n_1\,,\cdots,\,n_k$ is unity, then there exists a linear combination of these k numbers such that

$$a_1 n_1 + \cdots + a_k n_k = 1\,. \tag{3}$$

Separating equation (3) into a positive part and a negative part we have

$$\begin{aligned} &(a_{\alpha_1} n_{\alpha_1} + \cdots + a_{\alpha_l} n_{\alpha_l}) \\ &- (a_{\beta_1} n_{\beta_1} + \cdots + a_{\beta_{k-l}} n_{\beta_{k-l}}) = 1. \end{aligned} \tag{4}$$

If we designate

$$P = \sum_{j=\alpha_1}^{\alpha_l} a_{\alpha_j} n_{\alpha_j}; \qquad Q = \sum_{j=\beta_1}^{\beta_{k-l}} a_{\beta_j} n_{\beta_j}, \tag{5}$$

we can write equation (4) as follows:

$$P - Q = 1\,, \tag{6}$$

which tells us that $(P, Q) = 1$.

Denoting a complete set of residues of Q by $C_1, \cdots, C_Q$, we can form the products $C_1P, \cdots, C_QP$, which again give a complete set of residues of Q. From equation (5) we can see that $P \varepsilon \mathcal{R}_k$ and $Q \varepsilon \mathcal{R}_k$ (taking respectively in the expression for $\mathcal{R}_k$ the values $i_{\beta_j} = a_{\beta_j} = 0$, $i_{a_j} = a_{a_j}$ and $i_{\beta_j} = a_{\beta_j}, i_{a_j} = a_{a_j} = 0$). In the expression for $\mathcal{R}_k$, the i's range over all non-negative integers so that the multiples C_mP are also in $\mathcal{R}_k (i_{\beta_j} = a_{\beta_j} = 0, i_{a_j} = C_m a_{a_j})$. This gives a complete set of residues modulo $Q (C_1P, \cdots, C_QP)$ all of whose members are in $\mathcal{R}_k$. Now by allowing $i'_{\beta_j} = ia_{\beta_j}$, $(i = 1, 2, \cdots)$, we can add all non-negative multiples of Q to this set of residues, thereby building up all the integers that are greater than a certain integer N (in this case $N = (P - Q)(Q - P)$) as members of $\mathcal{R}_k$. This completes the proof.

In the following we will use the term "N-value" for any integer in $\mathcal{R}_k$ that is greater than or equal to an N satisfying Theorem I. When $(n_1, \cdots, n_k) = d \geqq 1$ we have the following

Corollary I. Given that:

1. $\mathcal{R}_k = \{i_1n_1 + \cdots + i_kn_k\}; \quad (i_j = 0, 1, 2, \cdots)$,
2. $(n_1, \cdots, n_k) = d$,
3. $\bar{\mathcal{R}}_k = Df \hat{N}' ((n_1, \cdots, n_k) = d \cdot N' \varepsilon \mathcal{R}_k \rightarrow N' + d \varepsilon \mathcal{R}_k)$,

then

$$m \varepsilon \bar{\mathcal{R}}_k \equiv m = N + id.i \geqq 0.N \varepsilon \mathcal{R}_k .$$

Proof: Factoring expression (1) of the hypothesis we have

$$\mathcal{R}_k = d\{i_1n_1' + \cdots + i_kn_k'\} . \tag{7}$$

The expression in brackets by Theorem I contains all integers greater than at least one integer N_1. Multiply N_1 and all greater integers by d and obtain $dN_1, dN_1 + d, \cdots$ and no others. With $N = dN_1$ we see they are all of the form $N + id$, which proves the theorem.

Theorem II. Given:

1. $\mathcal{R}_k = \{i_1n_1 + \cdots + i_kn_k\}$,
2. $(n_1, \cdots, n_k) = d$,
3. $n_l < n_{j \neq l}$,

then

1. $- (E \alpha, \beta) (\alpha \varepsilon \mathcal{R}_k . \beta \varepsilon \mathcal{R}_k . |\alpha - \beta| < d . \alpha \neq \beta)$,

2. $-(E\,\alpha\,,\beta)\,(\alpha\,\varepsilon\,\mathcal{R}_k.\,\beta\,\varepsilon\,\mathcal{R}_k.\,|\alpha-\beta|>n_l)$,

where $\alpha\,,\beta$ are consecutive.
Conclusion (2) is obvious from the definition of $\mathcal{R}_k$ and condition (3) of the theorem. To prove conclusion (1) assume that there are two distinct numbers α and β such that $|\alpha-\beta|<d$.

Designate them by

$$\alpha=a_1n_1+\cdots+a_kn_k\,,$$
$$\beta=b_1n_1+\cdots+b_kn_k\,,$$

so that

$$|\alpha-\beta|=|\,a_1n_1+\cdots+a_kn_k-(b_1n_1+\cdots+b_kn_k)\,|$$
$$=d|n_1'(a_1-b_1)+\cdots+n_k'(a_k-b_k)\,|\,.$$

From this we see that $-[|\alpha-\beta|<d]$ unless $a_i=b_i$ which contradicts the hypothesis that α and β are different.

Corollary I. Given two circuits of type shown in Figure 1 such that circuit I has an N-value of N_I and cycles of $n_1\,,\cdots,n_k$ and circuit II has an N-value of N_{II} and cycles of $m_1\,,\cdots,m_k$, then if $n_i=dm_i$ for all pairs of consecutive pairs $\alpha_1\,,\beta_1>N_I$ and $\alpha_2\,,\beta_2>N_{II}$ appearing in the response patterns of the circuits I and II, we have $|\alpha_1-\beta_1|=d|\alpha_2-\beta_2|$.

In other words the gaps in the case of circuit I are d times as great as those for II.

Proof: From Theorem II we have

$$|\alpha_1-\beta_1|=d_1|n_1'(a_1-b_1)+\cdots+n_k'(a_k-b_k)\,|$$
$$|\alpha_2-\beta_2|=dd_1|m_1'(a_1-b_1)+\cdots+m_k'(a_k-b_k)\,|\,.$$

Corollary II. Two circuits I and II similar to ones considered in Corollary I such that $(n_1\,,\cdots,n_k)=(m_1\,,\cdots,m_k)$ are identical in their response patterns after some finite N-value is reached.

Theorem III. Given that:

1. $\mathcal{R}_2=\{i_1n_1+i_2n_2\}$,
2. $(n_1\,,n_2)=1$,
3. $\bar{\mathcal{R}}_2=Df\,\hat{N}'(i)\,(N'\,\varepsilon\,\mathcal{R}_k.\,i\geqq 0\rightarrow N'+i\,\varepsilon\,\mathcal{R}_k)$,

then $(\alpha)\,(\alpha\,\varepsilon\,\bar{\mathcal{R}}_2.\,N\,\varepsilon\,\bar{\mathcal{R}}_2.\,N\leqq\alpha\rightarrow N=(n_1-1)\,(n_2-1)$. This theo-

rem gives the smallest integer for which Theorem I is true when $k = 2$.

Proof: In $\mathcal{R}_2$ let i_1 run through the smallest positive complete set of residues modulo $n_2 (0, 1, \cdots, n_2 - 1)$. Then a complete set of residues mod n_2 is in $\mathcal{R}_2$ (where $i_2 = 0$). Now by varying i_2 we can get a complete set consecutive in $\mathcal{R}_2$ whose last member is $(n_2 - 1)(n_1)$. The first member of this set will be $(n_2 - 1)(n_1) - (n_2 - 1) = (n_2 - 1)(n_1 - 1)$. This is the smallest such N. We could interchange the subscripts 1 and 2 throughout and obtain the same result, because n_1 and n_2 are symmetric in $(n_2 - 1)(n_1 - 1)$.

Corollary I. Given:

1. $\mathcal{R}_2 = \{i_1 n_1 + i_2 n_2\}$,
2. $(n_1, n_2) = d$,

then the N of the theorem is given by

$$d\left(\frac{n_2}{d} - 1\right)\left(\frac{n_1}{d} - 1\right).$$

Proof: Let $n_2 = dn_2'$, $n_1 = dn_1'$ where $(n_1', n_2') = 1$. The smallest N for n_1', n_2' is $(n_1' - 1)(n_2' - 1)$. As $\mathcal{R}_2 = d\{i_1 n_1' + i_2 n_2'\}$ then the smallest N for $\mathcal{R}_2$ is $d(n_1' - 1)(n_2' - 1) = d\left(\frac{n_1}{d} - 1\right)\left(\frac{n_2}{d} - 1\right)$.

In the proof of Theorem I we allowed all of the i_j to run through all positive integers. Actually, this is not necessary as it gives numerous duplications. We can restrict all of the i_j's except one to finite ranges by the following.

Assuming again that $(n_1, \cdots, n_k) = d$, we obtain,

$$\begin{aligned} n_1 &= dn_1' \\ &\cdot \\ &\cdot \\ &\cdot \\ n_k &= dn_k'. \end{aligned} \tag{8}$$

So from this we see that

$$\frac{n_1}{n_1'} \prod_{l=1}^{k} n_l' = \cdots = \frac{n_k}{n_k'} \prod_{l=1}^{k} n_l', \tag{9}$$

as $\dfrac{n_j}{n_j'} = d$.

Therefore, if we restrict the i's of equation 1 by

$$(i_1 = 1, 2, \cdots) \; ; \left(i_{j\neq 1} = 1, 2, \cdots, \frac{\prod_{l=1}^{k} n_l'}{n_j'} \right),$$

we get the same members for $\mathcal{R}_k$ as before. To show this, we need only to show that any set $\mathcal{R}_k$ with these restrictions is equal to another $\mathcal{R}_k$ where one of the $i_{j\neq 1} > \prod_{l=1}^{k} n_l'/n_j'$. Let $0 \leqq \alpha < \frac{\prod_{l=1}^{k} n_l'}{n_j'}$.

$$\left\{ i_1 n_1 + \cdots + \left(\frac{\prod_{l=1}^{k} n_l'}{n_j'} + \alpha \right) n_j + \cdots + i_k n_k \right\}$$

$$= \{ i_1 n_1 + \cdots + d \prod_{l=1}^{k} n_l' + \alpha n_j + \cdots + i_k n_k \}.$$

By taking $i_1 = \prod_{l=1}^{k} n_l'/n_1'$, we see that the term $d \prod_{l=1}^{k} n_l'$ is already represented by the term $i_1 n_1$, $(i = 1, 2, \cdots)$. This is so for all cases where $i_{j\neq 1} > \prod_{l=1}^{k} n_l'/n_j'$. We could, however, take any of the i_j's to run through all the integers plus zero. It is not restricted to i_1.

If we generalize circuit C of Figure 1 to that of circuit C' of Figure 2, we will note that if we change the value of τ_s from that

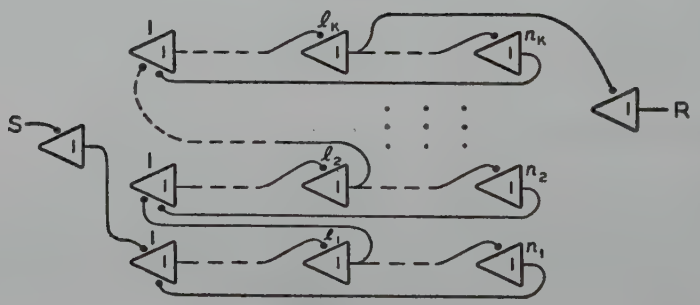

FIGURE 2

given on page 123 to $\tau_s = -[(k+2) + \sum_{i=1}^{k} l_j]$, then the same sequence $\mathcal{R}_k$ will hold for C' as for C. In other words, this generalization does nothing more than add $\sum_{i=1}^{k} l_j$ to all the members of the $\mathcal{R}_k$ for C.

This work was aided by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 10, 1948

AN ANALYSIS OF THEORETICAL SYSTEMS OF DIFFERENTIATING NERVOUS TISSUE

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Theoretical systems of neuroblasts differentiating according to various postulates are studied. The analysis determines the most likely patterns of connections implied by the differentiating systems. The exact expressions for the various parameters characterizing the resulting neural networks are approximated by simple analytic expressions which hold for systems having large numbers of neurons. The study is presented as a suggested approach to the more general problem of differentiating nervous systems.

Experimental studies of growing nerve tissue, particularly the work of P. Weiss (1934, 1947), have led to some understanding of the factors which influence the orientation of growing nerve fibers. These experiments are important validating evidence for the conjecture that in general the differentiating neuroblasts of growing nervous systems are not individually channelized into highly specific loci of growth, but that the factors which are responsible for nerve fiber orientation act regionally. These factors (such as the "ultrastructural organization" of the medium of growth discussed by Weiss) are of such a character that the regions effected are in general far greater than the dimensions of single nerve fibers. The factors controlling the average number of branches which will grow from each nerve fiber, the characteristic lengths and dispositions of those branches, and the factors determining the relative numbers of functional synapses which the fibers will form are still quite obscure.

If we grant that future work will lead to a greater understanding of the "growth orienting factors," "synapse forming factors," etc., involved in the process of neurogenesis, we can anticipate still another problem which will then arise, namely, what "kinds" of neural networks can be expected to develop as a result of such growth and differentiation factors. The general methods which may be developed to approach this problem will probably be somewhat independent of the specific details of the process.

More specifically, the problem is to:

1. Postulate an initial spacial distribution of neuroblasts.
2. State, in general terms, the factors which will act both spacially and temporally in the differentiation process.

3. Analytically derive the "types" and relative number of neural circuits which should arise as a consequence of such assumptions.

The problem as stated above, if carried out with biologically tenable assumptions, implies such prodigious mathematical obstacles as to be forbidding. For this reason it was chosen herein to begin with some very simple postulates, tentatively sacrificing biological plausibility for the sake of *developing the equations and "vocabulary" of the approach.* The method of analysis thereby developed may then be hoped to incorporate progressively more complicated and biologically tenable assumptions and thus slowly shed its purely theoretical character. Until such time as these latter developments materialize, therefore, discussions such as will follow in this paper must not be construed to depict any events occurring in actual developing nervous systems. Any judgment as to the utility of such efforts will have to be postponed until such time as their implications have been much more thoroughly investigated.

The Case of Two Aggregates

Distribution of Cycles. To begin with let us consider two aggregates (Fig. 1) of neuroblasts consisting of N_1 and N_2 cells respectively.

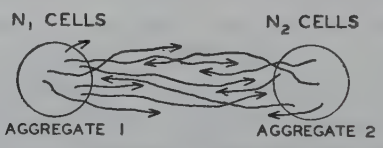

Figure 1

Let us assume that one non-branching fiber grows from each cell in each aggregate and is oriented to grow toward the cells of the opposing aggregate. Let us further assume that each of the growing fibers reaches the opposing aggregate and synapses on one of the cell bodies in that aggregate, the particular cell body being "chosen" at random. Note that these assumptions do not imply that each of the cell bodies will have at least one fiber synapsing on it, nor do they restrict the number of fibers which may synapse on any one cell body (aside from the restriction due to the finite number of fibers).

The first question to be considered is: What is the probability $C_1(1)$ that a neuron randomly selected from aggregate (1) will be a member of a one-pair cycle, i.e., connected to a cell body in aggregate (2) which cell sends a fiber to the same cell in (1). According

to our hypothesis the neuron randomly selected from aggregate (1) sends its fiber to some cell in aggregate (2). The probability that this cell in aggregate (2) sends its fiber back to the selected cell in (1) is $1/(N_1)$. Thus

$$C_1(1) = \frac{1}{N_1}. \tag{1}$$

Now let $C_1(n)$ be defined as the probability that a randomly selected cell in aggregate (1) is a member of an n-pair-cycle. By n-pair-cycle we mean a tandomly connected set of $2n$ cells forming a closed path alternating between aggregates (1) and (2). Figure 2

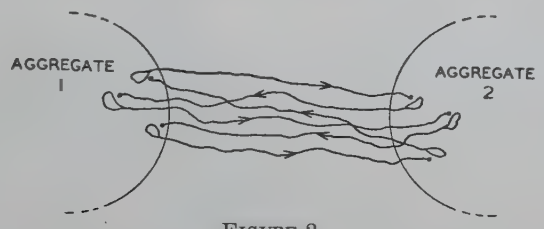

FIGURE 2

illustrates a 3-pair-cycle.

If we now ask for the probability $C_1(2)$ that a randomly selected cell in aggregate (1) is a member of a 2-pair-cycle, we can use the following argument. A randomly selected cell of (1) can be a member of a 2-pair-cycle if, and only if:

(a) The neuron in (2) to which it sends its fiber *does not* send one back to it.

(b) The neuron in (1) (third member of cycle) *does not* connect with the second member of the cycle in (2), and finally

(c) The fourth member of the cycle (whose cell body is in aggregate (2) sends its fiber to the originally selected cell of (1), thus completing the cycle.

The independent probabilities (a), (b), and (c) are

$$(N_1 - 1)/(N_1), \quad (N_2 - 1)/(N_2),$$

and $1/(N_1)$ respectively. The probability $C_1(2)$ of the occurrence of the composite event is therefore given by the product of the independent probabilities. Thus we obtain

$$C_1(2) = \frac{N_1 - 1}{N_1} \frac{N_2 - 1}{N_2} \frac{1}{N_1}. \tag{2}$$

By similar reasoning we obtain

$$C_1(3) = \frac{N_1-1}{N_1}\frac{N_2-1}{N_2}\frac{N_1-2}{N_1}\frac{N_2-2}{N_2}\frac{1}{N_1}, \tag{3}$$

and, in general,

$$C_1(n) = \frac{1}{N_1^{\,n} N_2^{\,n-1}} \times \overbrace{(N_1-1)(N_2-1)(N_1-2)(N_2-2)\cdots(N_1-n+1)(N_2-n+1)}^{2n-2 \text{ factors}}. \tag{4}$$

Having derived an expression for the probability that a randomly selected cell of aggregate (1) is specifically a member of an n-pair-cycle, we can now write an expression for the probability that a randomly selected cell of (1) is a member of any cycle at all. Since any one cell cannot be a member of more than one cycle, the probabilities $C_1(1), C_1(2), \cdots C_1(n)$ that it is a member of any specific size cycle are mutually exclusive. Thus the probability C_1 that a cell of (1) is a member of *any* cycle is the sum of those mutually exclusive probabilities. Hence we obtain for $N_1 < N_2$

$$C_1 = C_1(1) + C_1(2) + C_1(3) + \cdots + C_1(N_1). \tag{5}$$

We will refer to C_1 as the *cycle saturation* of aggregate (1).

Non-Cyclic Circuits. Neural connections other than cyclic can be expected to arise in the system. To illustrate the general disposition of neurons which are not members of cycles, we may resort to the following device. Imagine that the neurons are threads which are tied to each other wherever a synapse occurs. If we would now

FIGURE 3

pick a length of thread which represents the *last* neuron of a non-cyclic chain (one which synapses with a member of a cycle) and hold it aloft, we would find (typically) that it would carry with it not only a single chain of threads but the numerous side chains would also connect to it to form a "tree" of connections. Figure 3 illustrates such a "tree."

Having obtained an expression (equation 5) for the probability C_1 that a randomly selected neuron is a member of *any* cycle, we can now write an expression for the probability K_1 that a randomly selected neuron is a member of a tree. Since any cell which *is not* a member of a cycle is a member of a tree, we obtain for K_1

$$K_1 = 1 - C_1 . \tag{6}$$

Now let $K_1(k,n)$ be defined as the probability that a randomly selected cell of aggregate (1) is a "loose end" (has *no* connection leading *to* it) and is a member of a chain of neurons which after k links synapses to a neuron which is a member of an n-pair-cycle. Since $1/(N_1)$ is the probability that a particular neuron of aggregate (1) receives a connection from a particular neuron of aggregate (2), $1 - 1/(N_1)$ or $(N_1 - 1)/(N_1)$ is the probability that this connection is not made. Since aggregate (2) contains N_2 neurons, the probability that a particular neuron of aggregate (1) receives *no* connections from (2) is given by

$$\left(\frac{N_1 - 1}{N_1}\right)^{N_2} .$$

The probability that a particular neuron of (1) leads directly to an n-cycle is $C_2(n)$, hence the composite probability that a randomly selected neuron of (1) is a "loose end" which connects to an n-cycle is given by the expression

$$K_1(1,n) = \left(\frac{N_1 - 1}{N_1}\right)^{N_2} C_2(n). \tag{7}$$

If we now let $N_1 = N_2$ and drop all subscripts, by a similar argument we obtain

$$\begin{aligned} K(1,n) &= \left(\frac{N-1}{N}\right)^{N} C(n) \\ K(2,n) &= \left(\frac{N-1}{N}\right)^{N} (1-C)C(n) \\ K(3,n) &= \left(\frac{N-1}{N}\right)^{N} (1-C)^2 C(n) \\ &\cdots \\ K(k,n) &= \left(\frac{N-1}{N}\right)^{N} (1-C)^{k-1} C(n) . \end{aligned} \tag{8}$$

Similarly we can ask the following: What is the probability $K(k)$ that a randomly selected neuron is a "loose end" which after k "links" leads to *any* cycle? Arguing as before, we obtain

$$\begin{aligned} K(1) &= \left(\frac{N-1}{N}\right)^N C \\ K(2) &= \left(\frac{N-1}{N}\right)^N (1-C)C \\ &\vdots \\ K(k) &= \left(\frac{N-1}{N}\right)^N (1-C)^{k-1} C. \end{aligned} \tag{9}$$

Note that

$$\frac{K(k,n)}{K(k)} = \frac{C(n)}{C}.$$

As N grows large, the actual number (L) of "loose ends" in both aggregates approaches the product of the probability that any one cell is a loose end and the total number of cells in both aggregates. That is, for large N

$$L = 2N\left(\frac{N-1}{N}\right)^N. \tag{10}$$

On the other hand, the total number (T) of "trees" in the system is given by the total number of neurons which are connected to cycles, but which *are not* members of cycles themselves. Hence we obtain

$$T = 2N(1-C)C. \tag{11}$$

The average number (B) of "terminal branches" in each tree can then be written as the ratio of L to T. Thus

$$B = \left(\frac{N-1}{N}\right)^N \frac{1}{(1-C)C}. \tag{12}$$

The exact expressions for the various probabilities thus far derived are written in general as series which for large values of N are cumbersome to evaluate and difficult to interpret. It can be shown, however, that for large values of N these series asymptotically approach expressions of a much simpler character.

We will begin by writing the expression for the cycle saturation of the system in which $N_1 = N_2$ (equation (5) without subscripts)

$$C = C(1) + C(2) + \cdots + C(N). \tag{13}$$

Referring to equation (4) we can rewrite expression (13) as follows:

$$C = \frac{1}{N} + \frac{(N-1)^2}{N^3} + \frac{(N-1)^2(N-2)^2}{N^5} + \cdots + \frac{[(N-1)!]^2}{N^{2N-1}}. \tag{14}$$

By multiplying both members of (14) by N, factoring out

$$[(N-1)!]^2/N^{2N-2}$$

and writing the terms of the series in reverse order, we obtain

$$NC = \frac{[(N-1)!]^2}{N^{2N-2}}\left[1 + N^2 + \frac{N^4}{2!2!} + \cdots + \frac{N^{2N-2}}{[(N-1)!]^2}\right]. \tag{15}$$

Now let

$$E_2(N) = 1 + N^2 + \frac{N^4}{2!2!} + \frac{N^6}{3!3!} + \cdots + \frac{N^{2N-2}}{[(N-2)!]^2}, \tag{16}$$

where the notation $E_2(N)$ was so chosen because the terms are the squares of the terms of the exponential series $E(N)$. Then since

$$\frac{[(N-1)!]^2}{N^{2N-2}} = \frac{(N!)^2}{N^{2N}}, \tag{17}$$

we obtain

$$NC = \frac{(N!)^2}{N^{2N}} E_2(N). \tag{18}$$

By applying Stirling's formula to the coefficient of $E_2(N)$ in expression (18) we obtain

$$\frac{(N!)^2}{N^{2N}} = \frac{2\pi N}{e^{2N}}. \tag{19}$$

Thus equation (18) becomes

$$NC = \frac{2\pi N}{e^{2N}} E_2(N), \tag{20}$$

which reduces to

$$C = \frac{2\pi}{e^{2N}} E_2(N). \tag{21}$$

A typical term of the series $E_2(N)$ for a given N can be written as

$$f(k) \equiv \frac{N^{2k}}{(k!)^2}. \tag{22}$$

By applying Stirling's approximation formula to the typical term we obtain

$$f(k) = \frac{1}{2\pi} e^{2k} N^{2k} k^{-2k-1} e^{-\frac{\theta}{6k}}, \quad 0 < \theta < 1. \tag{23}$$

Let $\phi(k) = N^{2k} k^{-2k-1}$ then taking the natural logarithm of both members we obtain

$$ln\, \phi(k) = 2k\, ln\, N - (2k+1)\, ln\, k. \tag{24}$$

Let $k = N(1+t)$, $t = \frac{k}{n} - 1$. Now equation (24) can be written

$$ln\, \phi(k) = 2N(1+t)\, ln\, N - [2N(1+t)+1]\, ln\, N\,(1+t), \tag{25}$$

which can be written as

$$ln\, \phi(k) = -ln\, N - [2N(1+t)+1]\, ln(1+t). \tag{26}$$

Now letting $Z = 1 + t$ and $p(Z) = (2NZ + 1)\ ln\ Z$, by differentiation we obtain

$$\begin{aligned} p'(Z) &= 2N\, ln\, Z + (2N + \tfrac{1}{2}) \\ p''(Z) &= 2\frac{N}{Z} - \frac{1}{Z^2} \\ p'''(Z) &= \frac{2}{Z^2}(\tfrac{1}{2} - N). \end{aligned} \tag{27}$$

By expanding the right-hand member of equation (26) in Taylor series (with remainder) with reference to equations (27) we obtain

$$\begin{aligned} ln\, \phi(k) = -ln\, N - \Big\{ & p(1) + \frac{1}{1!} p'(1)\, t + \frac{1}{2!} p''(1)\, t^2 \\ & + \frac{1}{3!} p'''(1+\eta t) t^3 \Big\}, \end{aligned} \tag{28}$$

where $0 < \eta < 1$. Expression (28) can be written as

$$\ln \phi(k) = -\ln N - (2N+1)t - \tfrac{1}{2}(2N-1)t^2 - \frac{1}{6}p'''(1+\eta t)t^3. \tag{29}$$

Returning to equation (23) and referring to equation (29) we can write

$$f(k) = \frac{1}{2\pi} e^{2N(1+t)} \cdot \frac{1}{N} e^{-(2N-1)t - \frac{1}{2}(2N-1)t^2} \cdot \mu(k) \tag{30}$$

where

$$\mu(k) \equiv e^{-\frac{\theta}{6k} - \frac{1}{3}p'''(1+\eta t)t^2}.$$

Rewriting expression (30) we obtain

$$f(k) = \frac{1}{2N} e^{2N} \cdot e^{-t - \frac{1}{2}(2N-1)t^2}, \tag{31}$$

which can be simplified to read

$$f(k) = \frac{1}{2\pi N} e^{2N} \cdot e^{-Nt^2} \cdot e^{-t + \frac{1}{2}t^2} \cdot \mu(k). \tag{32}$$

Note that in the expression for $\mu(k)$, θ depends upon N, and that for large N, $\mu(k)$ approaches unity. Thus we obtain

$$E_2 N = \sum_0^N f(k) \simeq \frac{1}{2\pi N} e^{2N} \sum_0^N e^{-\frac{(k-N)^2}{N}}; \tag{33}$$

$$E_2(N) \simeq \frac{1}{2\pi N} e^{2N} \int_0^N e^{-\frac{(k-N)^2}{N}} dk. \tag{34}$$

But the integral of expression (34) can be written as

$$\frac{1}{2\pi N} e^{2N} \int_0^N e^{\frac{(k-N)^2}{N}} dk. \tag{35}$$

Now letting

$$\alpha^2 = \frac{2(k-N)^2}{N}$$

we obtain

$$E_2(N) \simeq \frac{e^{2N}}{2\sqrt{2}\pi\sqrt{N}} \int_{-\sqrt{2N}}^0 e^{-\frac{1}{2}\alpha^2} \lambda\, \alpha. \tag{36}$$

For large N the lower limit goes to infinity, and the sum $F_2(N)$ asymptotically approaches the expression

$$E_2(N) = \frac{e^{2N}}{4\sqrt{\pi N}}. \tag{37}$$

Therefore for large N the cycle saturation C is given by the expression*

$$C = \tfrac{1}{2}\sqrt{\pi/N}. \tag{38}$$

Table I (below) indicates the accuracy of the approximate form (38) as compared to the exact form (14) even for small values of N. (Tabulated to three significant figures)

TABLE 1

N	1	2	3	4	5
exact form	1	.625	.498	.428	.382
approx. form	.887	.627	.512	.444	.396
% error	—11.3	.32	2.8	3.7	3.6

Returning now to equation (10), since

$$\lim_{N\to\infty}\left(\frac{N-1}{N}\right)^N = \frac{1}{e},$$

we can write a simple approximation for L. Thus for large N

$$L \simeq \frac{2}{e}N. \tag{39}$$

In words, as the number of neurons of the system increases indefinitely, the number of neurons which are members of trees approaches a certain fraction of the total number, namely, $\frac{1}{e}$. On the other hand, the *total number* of trees in the system equals the total number of "trunks" of such trees, that is, the number of neurons which are themselves not members of cycles, but are directly connected to neurons which are. This number, given by (11) is seen to approach

$$T = \sqrt{\pi N}. \tag{40}$$

The average number (B) of "terminal branches" in each tree (an indicator of the configuration of neurons *within* the trees, for large N) then reduces to the expression

* Cf. the analogous expression for the cycle saturation of a single aggregate in Rapoport (1948).

$$B \simeq \frac{2}{e\sqrt{\pi}}\sqrt{N}. \tag{41}$$

The Case of Three Aggregates

A logical extension of the case of two aggregates is the addition of another aggregate. This can be accomplished in two alternative ways which are illustrated in Figure 4.

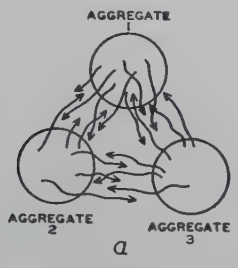

FIGURE 4*a*

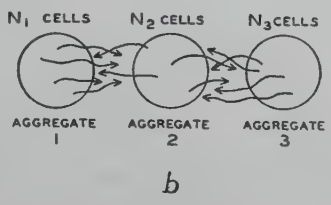

FIGURE 4*b*

This discussion will limit itself to the "linear" alternative illustrated in *B* of Figure 4, i.e., three aggregates linearly arranged with neuroblast numbering N_1, N_2 and N_3, terminal and central aggregates. Similar questions can be asked about this system as were asked about the two aggregate system. To begin with let $C_{ij}(n)$ be defined as the probability that a randomly selected cell of aggregate i is a member of a cycle which traverses the path $i \to j \to i$ n times. Using the same elementary probability considerations as were employed in dealing with the case of two aggregates, we arrive at the expression

$$C_{12}(n) = \left(\frac{1}{2}\right)^n \frac{1}{N_1^{\,n} N_2^{\,n-1}} \cdot \frac{\overbrace{2n-2 \text{ factors}}}{(N_1-1)(N_2-1)\cdots(N_1-n+1)(N_2-n+1)}. \tag{42}$$

Note that

$$C_{12}(n)_{\text{3 aggregates}} = \left(\frac{1}{2}\right)^n C_1(n)_{\text{2 aggregates}}. \tag{43}$$

The reason that the probabilities $C_{12}(n)$ and $C_1(n)$ differ by the factor $(\frac{1}{2})^n$ is that every time a cell of aggregate (1) (in the three aggregate case) leads to the central aggregate, the probability that the cell to which it connects will return to aggregate (1) is $\frac{1}{2}$, where-

as in the case of two aggregates the probability of return is unity (or certainty).

Because of the "asymmetry" of the connections to aggregate (1) and (2) we find that $C_{12}(n) \neq C_{21}(n)$, explicitly,

$$C_{21}(n) = \left(\frac{1}{2}\right)^n \frac{1}{N_1^{n-1} N_2^n} \frac{\overbrace{\qquad\qquad\qquad\qquad\qquad\qquad}^{2n-2 \text{ factors}}}{(N_1-1)(N_2-1)\cdots(N_1-n+1)(N_2-n+1)} \tag{44}$$

from which it follows that

$$C_{12}(n) = \frac{N_2}{N_1} C_{21}(n).$$

Finally if we consider the terminal aggregates (1 and 3) we obtain

$$C_{13}(1) = \frac{1}{2}\frac{N_2-1}{N_2}\frac{1}{2}\frac{1}{N_1}$$

$$C_{13}(2) = \frac{1}{2}\frac{N_2-1}{N_2}\frac{1}{2}\frac{N_1-1}{N_1}\frac{N_2-2}{N_2}\frac{N_3-1}{N_3}\frac{N_2-3}{N_2}\frac{1}{2}\frac{1}{N_1}$$

. . . (45)

$$C_{13}(n) = \left(\frac{1}{2}\right)^{2n} \frac{1}{N_1^n N_2^{2n} N_3^{n-1}} \overbrace{\qquad\qquad}^{n-1 \text{ factors}} \overbrace{(N_1-1)(N_1-2)\cdots(N_1-n+1)}$$

$$\overbrace{\qquad\qquad\qquad}^{2n-1 \text{ factors}} \overbrace{(N_2-1)\cdots(N_2-2n+1)} \quad \overbrace{\qquad\qquad}^{n-1 \text{ factors}} \overbrace{(n_3-1)\cdots(N_3-n+1)}.$$

If we drop the subscripts letting $N_1 = N_2 = N_3 = N$, we obtain a somewhat simpler expression for $C_{13}(n)$, namely,

$$C_{13}(n) = \left(\frac{1}{2}\right)^{2n} \frac{1}{N^{4n-2}} \overbrace{\qquad\qquad}^{n-1 \text{ factors}} \overbrace{(N-1)^3(N-2)^3\cdots(N-n+1)^3} \frac{\overbrace{\qquad\qquad\qquad\qquad}^{2n-1 \text{ factors}}}{(N-n)(N-n-1)\cdots(N-2n+1).} \tag{46}$$

Some interesting generalizations may be arrived at if this analysis were extended to a chain of k aggregates having N_1, $N_2 \cdots N_k$ cells per aggregate respectively.

Concluding Remarks.

The analysis presented here dealt with two very simple systems consisting of "neurons" which are capable of making only single connections.

Subsequent analysis should perhaps proceed by introducing the complication that each neural element can differentiate large numbers of branches many of which are capable of forming functional connections. Future work should also consider systems in which the geometry plays a significant role, thus making certain connections more probable than others. Gradations of "bias" can be imposed on the growth of the fibers until cases ranging from complete "randomness" to rigidly determined structures have been studied. A paper by A. Rapoport (1948) takes some significant steps in this direction.

The problem of choosing useful parameters by means of which a neural net can be characterized has already been met with in a previous paper (Shimbel and Rapoport, 1948). Suggestions for the improvement of nomenclature and selection of useful parameters will probably be determined largely by the dictates of future analysis.

The author wishes to thank Drs. A. Rapoport and L. J. Savage for their generous assistance and critical discussion of this paper.

This work was aided by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 10, 1948

CYCLE DISTRIBUTIONS IN RANDOM NETS

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Characteristics of random nets are derived from assumptions concerning the distribution of connections. The single aggregate of neurons with random connections without branching and two parallel chains with normal distribution of connections are considered. The cycle saturation is derived for each type of net, that is, the fraction of neurons which are members of cycles. It is shown that in the single aggregate with random connections, the cycle saturation varies inversely as the square root of the number of neurons; in the dense two-chain net it varies inversely as the square root of the neuron density and inversely on the square root of the standard deviation of the normal distribution.

I. *Introduction.*

The first attempts to consider the behavior of so-called "random neural nets" in a systematic way have led to a series of problems concerned with relations between the "structure" and the "function" of such nets. The "structure" of a random net is not a clearly defined topological manifold such as could be used to describe a circuit with explicitly given connections. In a random neural net, one does not speak of "this" neuron synapsing on "that" one, but rather in terms of tendencies and probabilities associated with points or regions in the net.

One could take the existence of such tendencies as one's starting point, and, by applying probabilistic dynamics based on the fundamental assumptions about the behavior of individual neurons (thresholds, synaptic delay, etc.) derive the *probable* characteristics of behavior for a net specified by certain parameters. Such has been the procedure in a recent paper by A. Shimbel and A. Rapoport (1948).

One could also proceed in another way. One could assume certain patterns of *development* for a net and then, again by applying probabilistic methods, deduce a probable *structure* for the resulting net, which, in turn, will imply certain characteristics of function. In the present paper, the latter approach will be used.

We are concerned with the formation of cycles in neural nets, that is, structures represented by the following chain

$$a \to b \to c \to \ldots\ldots \to a\,, \qquad (1)$$

where $a \rightarrow b$ signifies that neuron a sends an axone which synapses on neuron b, etc.

Cycles are of importance in the function of neural nets in the central nervous system, because they are the possible seats of permanent or semi-permanent activity. Given a cycle represented by the chain (1), it is evident that under the assumption that each neuron fires if, and only if, the neuron sending an axone to it fires, we shall have permanent activity in the cycle following the excitation of any of the neurons belonging to it.

Consider now a net in which a certain fraction of neurons are members of cycles, while the remainder are not. If we now suppose that at a given moment every neuron of the net fires once, then, following this initial activity (which is, let us say, imposed from the outside) there will be a certain *residual* permanent activity in the net, where the number of neurons involved will be the number of neurons which are members of cycles. Moreover, each such neuron will be firing with a certain frequency, depending on the number of neurons in the cycle of which it is a member.

If neurons are restricted to sending one and only one axone, then each neuron will be a member of at most one cycle. If, however, this restriction does not apply, then a neuron may be a member of several distinct cycles. Such a neuron will be subject to a composite frequency of excitation. Thus let the neurons in Figure 1 all have thres-

FIGURE 1

hold 1, and the synaptic delays all be equal. Then, if any one of the neurons fires, very soon every neuron will be firing repeatedly once per synaptic delay. Some aspects of such nets were discussed by J. B. Roberts (1948).

Problems involving neurons belonging to more than one cycle will not be considered here, inasmuch as we are considering one-axone nets throughout.

We define the *cycle saturation* of a net as the fraction of neurons in it which are members of cycles. By the *cycle distribution* we shall mean the sequence of fractions of the neurons of a one-axone net which are members of 2-cycles, $(a \rightarrow b \rightarrow a)$ 3-cycles $(a \rightarrow b \rightarrow c \rightarrow a)$, $\cdots$ s-cycles, etc. Thus the cycle saturation will determine the relative amount of residual activity in a net, following an initial stimulation, while the cycle distribution of a one-axone net

will give the distribution of the frequencies with which these permanently active neurons are firing.

II. *The Single Aggregate One-Axone Net with Random Connections.*

Consider a set of cells distributed in some region such that at a certain phase of their development, each cell sends an axone which eventually synapses on an arbitrary cell other than its own. Thus every cell sends an axone, but not necessarily every one receives one. Our aggregate of cells then becomes a single aggregate* one-axone neural net with random connections. In such a situation, if the number of cells is finite, cycles must arise. Thus a 2-cycle will arise if a neuron receiving an axone sends its axone to the cell from which it has received it, etc. If $N + 1$ is the number of neurons in the net, the probability that a neuron will synapse on some particular other neuron is $1/N$. Then the respective probabilities C_k of the occurrence of k-cycles will be given by

$$
\begin{aligned}
C_2 &= \frac{1}{N} \\
C_3 &= \frac{N-1}{N^2} \\
C_4 &= \frac{(N-1)(N-2)}{N^3} \\
&\vdots \\
C_k &= \frac{(N-1)(N-2)\cdots(N-k+2)}{N^{k-1}} \\
&\vdots \\
C_{N+1} &= \frac{(N-1)!}{N^N}.
\end{aligned}
\tag{2}
$$

Since the probabilities C_k are mutually exclusive, we get for the probability that a neuron is a member of *any* cycle (that is, the cycle saturation of the net)

* Multiple aggregate nets are discussed by A. Shimbel (1948).

$$C(N+1) = \sum_{k=2}^{N+1} C_k = \frac{1}{N} + \frac{N-1}{N^2} + \cdots \frac{(N-1)!}{N^N}. \tag{3}$$

For a small number of neurons, $N+1$, C can be directly computed. We have $C(2) = 1$, which means that if the aggregate consists of only two neurons, both must be members of (the) cycle. Similarly $C(3) = \frac{1}{2} + \frac{1}{4} = 3/4$, that is the probability of a neuron being a member of a cycle in an aggregate of three neurons is $3/4$; $C(4) = 17/27$; $C(5) = 37/64$; $C(6) = 1669/3125$, etc.

For large values of N, it will be more convenient to compute $NC(N+1)$. From (3), we have

$$\begin{aligned} NC &= 1 + \frac{N-1}{N} + \cdots \frac{(N-1)!}{N^{(N-1)}} \\ &= \frac{(N-1)!}{N^{(N-1)}} \left[1 + N + \frac{N^2}{2!} + \cdots \frac{N^{(N-1)}}{(N-1)!} \right]. \end{aligned} \tag{4}$$

If N is large, the quantity $(N-1)!/N^{(N-1)} = N!/N^N$ can be approximated by Stirling's formula

$$N!\, N^{-N} \sim \sqrt{2\pi N}\, e^{-N}. \tag{5}$$

Thus

$$NC \sim \sqrt{2\pi N}\, e^{-N} \left(1 + N + \frac{N^2}{2!} + \cdots \frac{N^{(N-1)}}{(N-1)!} \right). \tag{6}$$

To evaluate $e^{-N} \left(1 + N + \frac{N^2}{2!} + \cdots \frac{N^{(N-1)}}{(N-1)!} \right)$,

we use the formula*

$$\operatorname*{Lim}_{N\to\infty} e^{-N} \sum_{k=0}^{N-1} \frac{N^k}{k!} = \frac{1}{\sqrt{2\pi}} \int_0^\infty e^{-t^2/2}\, dt = 1/2.$$

Substituting this value into (6), we obtain $C = \sqrt{\pi/2N}$ and state our result in

Theorem 1. *In a large single aggregate one-axone net with random connections, the cycle saturation is given by*

$$C = \sqrt{\pi/2N}. \tag{7}$$

Corollary. The expected number of neurons which are members of cycles in such a net is

* For justification of this approximation see J. V. Uspenski (1937).

$$(N+1)C = \sqrt{\pi N/2} + \sqrt{\pi/2N} \sim \sqrt{\pi N/2}\,.$$

Comparing the exact expression (3) for $N = 5$ with this approximation, we have $1669/3125 \sim 0.53$, while $\sqrt{\pi/10} \sim 0.56$, that is the approximation formula gives C within 6 per cent even for an aggregate of six neurons.

III. *The Two-Chain Net with Normal Distribution of Connections.*

Consider next two parallel rows of cells, each of which sends one axone to some cell in the opposite row, as in Figure 2.

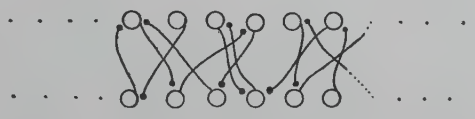

FIGURE 2

The probabilities of connections are assumed as follows: We will designate an arbitrary pair of cells lying opposite each other in the two chains as the origin and the abscissa of each cell (its directed distance from the origin cell in its own chain) by x for the upper row and y for the lower. Then the probability that the axone from x synapses on y or that the axone from y synapses on x will be assumed as

$$P(x, y) = \frac{\delta}{\sigma\sqrt{2\pi}}\, e^{\frac{-(x-y)^2}{2\sigma^2}}\,, \tag{8}$$

where δ is the distance between two successive cells in a row, and σ is the parameter of standard deviation in the normal probability distribution

$$w(t) = \frac{1}{\sigma\sqrt{2\pi}}\, e^{\frac{-t^2}{2\sigma^2}}\,.$$

It is assumed that δ is small compared to unity, so that the two chains can be considered as linear continua.

Our problem is to compute the cycle saturation of the net resulting from the connections occurring as described by equation (8). We will need the following

Lemma. *The quadratic form*

$$Q(r) = -x_1^2 + x_1x_2 - x_2^2 + x_2x_3 \cdots + x_{r-1}x_r - \tfrac{1}{2}x_r^2 \tag{9}$$

may be written as

$$-\left(x_1-\frac{1}{2}x_2\right)^2-\frac{3}{4}\left(x_2-\frac{2}{3}x_3\right)^2-\frac{4}{6}\left(x_3-\frac{3}{4}x_4\right)^2$$
$$-\cdots\cdots\frac{k+1}{2k}\left(x_k-\frac{kx_{k+1}}{k+1}\right)^2-\cdots\cdots-\tfrac{1}{2}rx_r^2. \tag{10}$$

Proof. The relation obviously holds for $r=2$. We will first establish an induction on the coefficient of the kth bracket. Suppose, therefore, that the kth term of (10) is given by $(k+1)\,[x_k-kx_{k+1}/(k+1)]^2/2k$, and let us compute the $(k+1)$th term. If the kth bracket of (10) is expanded, the coefficient of x^2_{k+1} will be $(k+1)k^2/2k(k+1)^2=k/2(k+1)$. But the coefficient of x^2_{k+1} in (9) is unity. Therefore an additional x^2_{k+1} term must appear in (10) with coefficient equal to $1-k/2(k+1)=(k+2)/2(k+1)$, and that is the coefficient of the $(k+1)$th bracket. This proves the induction on the bracket coefficients.

To prove our contention concerning the coefficients of the second terms within the brackets, we note that in the expansion of the kth bracket of (10), the coefficient of the cross-product will be

$$a_{k+1}(k+1)/k,$$

where a_{k+1} is the coefficient of x_{k+1} within the kth bracket. But the coefficient of x_kx_{k+1} in (9) is unity. Hence $a_{k+1}=k/(k+1)$ as desired.

Finally the coefficient x_r^2 coming from the last bracket of (10) is $(r-1)/2r$, and it is $1/2$ in (9). Hence the coefficient of the last term in (10) must be $1/2-(r-1)/2r=\frac{1}{2}r$ as desired. This proves the lemma.

Before we proceed to the computation of the cycle saturation of our net, we will first consider an

Associated Random Walk Problem.

Let a particle suffer displacements from cell to cell, such that each displacement is always to a cell in the opposite row, and let the probability of each displacement be given by equation (8). We seek the probability that after $2s$ displacements the particle returns to its original position.

Theorem 2. *The probability of return to original position after* 2s *displacements in the associated random walk problem is given by*

$$Z_s=\frac{\delta}{2\sigma\sqrt{\pi s}}\left[1-\frac{\delta^2}{12s}+\frac{\delta^4}{64s^2}\cdots\right]. \tag{11}$$

Proof. Without loss of generality we can suppose that the particle starts its random walk at the origin in the upper row. Then,

denoting by x's points in the upper row and by y's those of the lower and considering the two chains as continua, we have

$$Z_s = \frac{1}{\sigma^{2s}(2\pi)^s} \underbrace{\int_{-\delta/2}^{\delta/2} \cdots \int_{-\infty}^{\infty} \int_{-\infty}^{\infty}}_{2s} \mathrm{Exp}\left\{ \frac{1}{2\sigma^2} \times [-y_1^2 - (y_1 - x_1)^2 - (x_1 - y_2)^2 \cdots - x_s^2] \right\} dy_1\, dx_1\, dy_2 \cdots dx_s\,. \tag{12}$$

Note that the polynomial in the exponential bracket may be written as

$$\sigma^{-2}(-y_1^2 + y_1 x_1 - x_1^2 + x_1 y_2 - \cdots - \tfrac{1}{2} x_s^2) \tag{13}$$

that is essentially as the quadratic form (9), which by our lemma may be written in the form of (10). Therefore

$$Z_s = \frac{1}{\sigma^{2s}(2\pi)^s} \int_{-\delta/2}^{\delta/2} \cdots \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \mathrm{Exp}\left\{ \sigma^{-2} \left[-\left(y_1 - \frac{1}{2} x_1 \right)^2 - \frac{3}{4} \left(x_1 - \frac{2}{3} y_2 \right)^2 \cdots - \frac{1}{4s} x_s^2 \right] \right\} dy_1\, dx_1 \cdots dx_s. \tag{14}$$

All the terms of the exponential after the first one are independent of y_1; all the terms after the second are independent of x_1, etc. The integrations can therefore be performed on the exponential functions of the type

$$e^{\frac{-a_i (x-y)^2}{2}} \quad (a_i = 1, 2 \cdots 2s-1). \tag{15}$$

Each infinite integral of this type yields a factor, $\sigma\sqrt{\pi/a_i}$, and we obtain, after performing all the infinite integrations,

$$Z_s = \frac{1}{\sigma^{2s}(2\pi)^s} \sigma^{2s-1} \pi^{\frac{1}{2}(2s-1)} \prod_{i=1}^{2s-1} (a_i)^{-\frac{1}{2}} \times \int_{-\delta/2}^{\delta/2} e^{-x_s^2/4s}\, dx_s. \tag{16}$$

Furthermore,

$$\prod_{i=1}^{2s-1} (a_i)^{-\frac{1}{2}} = \left(\frac{2}{2} \cdot \frac{4}{3} \cdot \frac{6}{4} \cdots \frac{4s-2}{2s} \right)^{\frac{1}{2}} = 2^{s-1} s^{-\frac{1}{2}}. \tag{17}$$

Hence,

$$Z_s = \frac{1}{\sigma\sqrt{\pi s}} \int_{-\delta/2}^{\delta/2} e^{-x_s^2/4s}\, dx_s. \tag{18}$$

Expanding the integrand in series, integrating term by term, and factoring out δ, we finally obtain

$$Z_s = \frac{\delta}{\sigma\sqrt{\pi s}}\left[1 - \frac{\delta^2}{12s} + \frac{\delta^4}{64s^2} \cdots\right].$$

This proves the theorem.

For $\delta << 1$, as assumed above, the result reduces to

$$Z_s = \frac{\delta}{\sigma\sqrt{\pi s}}. \tag{19}$$

Computation of Cycle Distribution.

The quantities Z_s (except Z_1) do not give the probabilities of the corresponding types of cycles. Consider Z_2 as the probability that the origin sends an axone to a cell at y_1 in the lower row, which sends one to x_1 in the upper row, which sends to y_2, which sends to 0. This situation will describe a 2-pair cycle only if $x_1 \neq 0$; $y_1 \neq y_2$. For suppose that $x_1 = 0$. Then the firing of y_1 will imply the firing of 0, which will again fire y_1, and we shall have a 1-pair cycle only. The neuron at y_2 will never fire under these conditions. A similar situation will result if $y_1 = y_2$. In general, the scheme

$$0 \to y_1 \to x_1 \to y_2 \to x_2 \to \cdots y_s \to 0 \tag{20}$$

will be an s-pair cycle only if all the x's are distinct and not equal to zero, and all the y's are distinct. That is to say, the path (20) will be an s-pair cycle, if, and only if, none of its neurons are members of cycles of order less than s.

If we denote by C_s the probability of occurrence of an s-pair cycle, we have

$$C_1 = Z_1; \quad C_s < Z_s \quad (s > 1). \tag{21}$$

We seek to express the C_s in terms of the Z_s. To do this, let us first compute C_2.

The expression for C_2 will be quite similar to that for Z_2 in equation (12) except that the infinite integrals will be taken not over the entire infinite interval $(-\infty, \infty)$ but over a *selected set of points*, namely, over those points in the interval where cells which are *not* members of one-pair cycles are located. Since we may suppose that

cells which are members of different cycles are uniformly distributed over the whole infinite integral, the restriction of the domain of integration means merely the reduction of the Lebesgue measure of each unit interval from unity to the Lebesgue measure of the set of points which are not members of one-pair cycles. The Lebesgue measure in a unit interval of such points will be $1 - C_1$. Since three of the variables (y_1, x_1, x_2) are restricted to these point sets, we shall obtain C_2 if we "weight" the integrand of (12) with the factor $(1 - C_1)$ three times, that is

$$C_2 = \frac{(1-C_1)^3}{2\pi\sigma^4} \int_{-\delta/2}^{\delta/2} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \operatorname{Exp}\left\{ \frac{1}{2\sigma^2} \right.$$

$$\left. \times (-y_1^2 - (y_1 - x_1)^2 - (x_1 - y_2)^2 - x_2^2 \right\} dy_1 \cdots dx_2 \qquad (22)$$

$$= (1 - C_1)^3 Z_2 .$$

Similarly,

$$C_3 = [1 - (C_1 + C_2)]^5 Z_3 , \qquad (23)$$

and in general

$$C_s = \left[1 - \sum_{i=1}^{s-1} C_i \right]^{2s-1} Z_s . \qquad (24)$$

Equation (24) gives an iteration formula for the C's, where C_s, we recall, is the probability of an s-pair cycle. Since the probabilities of each type of cycle are mutually exclusive, we obtain for the cycle saturation of our net

$$C = \sum_{s=1}^{\infty} \left[1 - \sum_{i=1}^{s-1} C_i \right]^{2s-1} Z_s . \qquad (25)$$

Computation of Cycle Saturation.

We are now prepared to compute the cycle saturation in terms of the parameters of our net (δ and σ). Since the Z_s are easily expressed in terms of these parameters, cf. equation (19), we will express C in terms of the Z's.

Theorem 3. *Let the sequence of quantities* $\mathbf{z}^{(j)}$ *be defined as follows:*

$$\begin{aligned} z^0 &= 1 \\ z' &= 1 - Z_1 \\ z'' &= z'(1 - z'^2 Z_2) \\ z''' &= z''(1 - z''^4 Z_3) \\ &\cdot \\ &\cdot \\ &\cdot \\ z^{(j)} &= z^{(j-1)} [1 - (z^{(j-1)})^{2j} Z_j] . \end{aligned} \tag{26}$$

Then the cycle saturation of the two-chain net with normal distribution of connections will be given by

$$C = \sum_{j=1}^{\infty} (z^{(j-1)})^{2j-1} Z_j = Z_1 + z'^3 Z_2 + z''^5 Z_3 + \cdots . \tag{27}$$

Proof. We have seen that $C_1 = Z_1$. By the iteration formulae (24) and (26), we have

$$C_2 = (1 - Z_1)^3 Z_2 = z'^3 Z_2$$

$$C_3 = (1 - Z_1 - z'^3 Z_2)^5 Z_3 = (z' - z'^3 Z_2)^5 Z_3 = z''^5 Z_3$$

$$\begin{aligned} C_4 &= (1 - Z_1 - z'^5 Z_2 - z''^5 Z_3)^7 Z_4 \\ &= (z' - z'^3 Z_2 - z''^5 Z_3)^7 Z_4 = z'''^7 Z_4 , \text{ etc.} \end{aligned}$$

Summing over the C's we obtain (27). This proves the theorem.

Corollary. *If the approximation* (19) *is used for the* Z's, *the expression for the cycle saturation of a two-chain net becomes*

$$\begin{aligned} C &= \frac{\delta}{2\sigma\sqrt{\pi}} \left(1 + \frac{(z')^3}{\sqrt{2}} + \frac{(z'')^5}{\sqrt{3}} + \cdots \right) \\ &= \frac{\delta}{2\sigma\sqrt{\pi}} \sum_{j=1}^{\infty} \frac{[Z^{(j-1)}]^{2j-1}}{\sqrt{j}} . \end{aligned} \tag{29}$$

Remark. The series in (27) converges, because it is dominated by the geometric* series $\sum_{n=1} (z')^n$. This is true, because the $z^{(j)}$ form a monotone decreasing sequence of positive terms, all less than unity, while the denominators of (29) further decrease the absolute value of each term.

However note that the series converges very slowly, since the first several numerators are very close to unity, so that at first the

* Geometric because $z' = 1 - Z_1 < 1$.

series behaves like the divergent series $\sum_{n=1}^{\infty} \frac{1}{\sqrt{n}}$.

One may get an upper bound on C by noting that

$$C \leqq \frac{\delta}{2\sigma\sqrt{\pi}}\left[1+\sum_{j=2}^{\infty}\frac{(z')^{2j-1}}{\sqrt{j}}\right]. \tag{30}$$

Evaluation of $\sum_{j=2}^{\infty}\frac{(z')^{2j-1}}{\sqrt{j}}$.

Let $(z')^2 = R$. Then

$$\sum_{j=2}^{\infty}\frac{(z')^{2j-1}}{\sqrt{j}} = \frac{1}{z'}\sum_{j=1}^{\infty}\frac{R^j}{\sqrt{j}}. \tag{31}$$

We will evaluate $\sum_{j=1}^{\infty}\frac{R^j}{\sqrt{j}}$. Note that this series is dominated by the integral $\int_0^{\infty}\frac{R^x}{\sqrt{x}}\,dx$. Let $x = (-\log_R e)y$.

Then

$$\begin{aligned}\int_0^{\infty}\frac{R^x}{\sqrt{x}}\,dx &= \int_0^{\infty} e^{-y}(-\log_R e)^{\frac{1}{2}}\,y^{-\frac{1}{2}}\,dy \\ &= (-\log_R e)^{\frac{1}{2}}\,\Gamma(1/2) = (-\log_R e)^{\frac{1}{2}}\sqrt{\pi} \qquad (32)\\ &= \sqrt{\pi(-\log_R e)} = \frac{\sqrt{\pi}}{\sqrt{-\log_e R}}.\end{aligned}$$

Therefore

$$\sum_{j=2}^{\infty}\frac{(z')^{2j-1}}{\sqrt{j}} \sim \frac{1}{z'}\frac{\sqrt{\pi}}{(-\log_e R)^{\frac{1}{2}}} = \frac{1}{z'}\frac{\sqrt{\pi}}{\sqrt{2}(-\log_e z')^{\frac{1}{2}}}, \tag{33}$$

and we have

Theorem 4. *For small values of* δ *(and therefore of* Z_1*) an upper bound on* C, *which near* $Z_1 = 0$ *is also an approximation, is given by*

$$C \sim Z_1\left[1+\frac{\sqrt{\pi}}{\sqrt{2}(1-Z_1)\,(-\log_e[1-Z_1])^{\frac{1}{2}}}\right]. \tag{34}$$

Remarks. When $Z_1 << 1$, the second term in the brackets of

(34) is very large compared to unity. An approximation of C may then be given by

$$C \sim \sqrt{\frac{\pi}{2}} \frac{Z_1}{(1-Z_1)[-\log(1-Z_1)]^{\frac{1}{2}}}. \tag{35}$$

Note that C is a function of Z_1 and therefore of δ/σ. However, we may write C as a function of our original parameters, δ and σ, by substituting the value of Z_1 given by (19). Thus we obtain

$$C \sim \frac{\delta}{2\sqrt{2}\sigma(1-\delta/2\sigma\sqrt{\pi})[\log(2\sigma\sqrt{\pi}) - \log(2\sigma\sqrt{\pi}-\delta)]^{\frac{1}{2}}}. \tag{36}$$

The Behavior of Cycle Saturation and Cycle Density for Large Neuron Density.

The *neuron density* and the *cycle density* of a chain net may be naturally defined as $1/\delta$ and C/δ respectively. When $\delta << 1$, the neuron density is large.

If we assume that also $\delta << \sigma$, that is Z_1 is small (which assumption underlies the whole treatment of the chain net), we can approximate C in the vicinity of $\delta = 0$ by expanding the functions of Z_1 involved in expression (35). Thus

$$-\log(1-Z_1) \sim Z_1(1+\tfrac{1}{2}Z_1)$$

$$\left[-\log(1-Z_1)\right]^{-\frac{1}{2}} \sim Z_1^{-\frac{1}{2}}\left(1-\frac{Z_1}{4}+\frac{3Z_1^2}{32}+\cdots\right)$$

$$(1-Z_1)^{-1} \sim 1+Z_1+Z_1^2+\cdots \tag{37}$$

$$C \sim \sqrt{\frac{\pi}{2}}\sqrt{Z_1}(1+Z_1+Z_1^2+\cdots)\left(1-\frac{Z_1}{4}+\frac{3Z_1^2}{32}+\cdots\right)$$

$$C \sim \sqrt{\frac{\pi Z_1}{2}}.$$

Substituting for Z_1 its value given by (19), we obtain

$$C \sim \frac{\pi^{1/4}}{2}\sqrt{\frac{\delta}{\sigma}}$$

$$C/\delta \sim \frac{\pi^{1/4}}{2}\sqrt{\frac{1}{\delta\sigma}}.$$

We embody these results in our final

Theorem 5. *For large densities of neurons* ($\delta << 1$ and $\delta << \sigma$) *the cycle saturation of a two-chain net with normal distribution of connection probabilities is approximately proportional to* $(\delta/\sigma)^{\frac{1}{2}}$, *while the cycle density is approximately proportional to* $(\delta\,\sigma)^{-\frac{1}{2}}$, *the constant proportionality being* $\frac{1}{2}\pi^{1/4}$.

Corollary. *The cycle saturation of a dense two-chain net varies inversely as the square root of the product of neuron density and standard deviation.*

The author wishes to acknowledge his thanks to Dr. L. J. Savage for a critical discussion of this paper.

This work was aided by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 10, 1948

ON PERIODICITIES IN METABOLIZING SYSTEMS

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Following a previous study by A. Weinberg, the author investigates periodical diffusion phenomena produced in a spherical cell by a simple coupled set of chemical reactions. The general solution even for a spherical cell does not possess spherical symmetry. It is found that periodic oscillations are possible with a frequency spectrum determined by a set of "eigenvalues." However, these oscillations are all damped even if the system of coupled reactions which is responsible for them has nondamped solutions. Therefore, although very complex and highly asymmetrical configurations of concentrations may be thus produced in the cell, none of those configurations, except some possible centrally symmetric ones, is lasting.

Following a suggestion by the author (Rashevsky, 1938, chap. vi; 1948, chap. vi), Alvin M. Weinberg (1938) studied periodical diffusion phenomena produced in a spherical cell by a simple coupled reaction. He limited himself, however, to solutions which possess spherical symmetry. The periodicities are due to the fact that a system of two first-order differential equations is formally equivalent to a single differential equation of second order. This problem formally resembles, therefore, the problem of elastic vibrations. In the cases of elastic vibrations a system with central symmetry, for instance, a circular membrane or disk, possesses stable solutions which do not have central symmetry. It is therefore of interest to investigate the possibility of a similar situation arising in the case of periodical diffusion fields, and whether, as a result, all kinds of nonsymmetric diffusion configurations might appear in a spherical cell.

We shall denote by c_{i1} and c_{i2} the concentrations of the two reacting substances inside of the cell, and by c_{e1} and c_{e2} the corresponding concentrations outside of the cell. At an infinite distance from the cell c_{e1} and c_{e2} reduce to c_{01} and c_{02}. The diffusion coefficients for the two substances inside of the cell are denoted by D_{i1} and D_{i2}, while outside of the cell they are denoted by D_{e1} and D_{e2}. The permeabilities of the cell membrane are h_1 and h_2. Denoting by a_{11}, a_{12}, a_{21}, and a_{22} four constants, which may be positive or negative, we assume the following expressions for the rates of production q_1 and q_2 per unit volume of the two substances inside of the cell:

$$q_1 = a_{11}c_{i1} + a_{12}c_{i2} \; ; \qquad q_2 = a_{21}c_{i1} + a_{22}c_{i2} \, . \tag{1}$$

Denoting by ∇^2 the Laplacian operator, we find for the diffusion equations inside of the cell:

$$\frac{\partial c_{i1}}{\partial t} = D_{i1}\nabla^2 c_{i1} + a_{11}c_{i1} + a_{12}c_{i2} \; ; \qquad \frac{\partial c_{i2}}{\partial t} = D_{i2}\nabla^2 c_{i2} + a_{21}c_{i1} + a_{22}c_{i2} . \tag{2}$$

Outside of the cell we have

$$\frac{\partial c_{e1}}{\partial t} = D_{e1}\nabla^2 c_{e1} \; ; \qquad \frac{\partial c_{e2}}{\partial t} = D_{e2}\nabla^2 c_{e2} . \tag{3}$$

At the boundary we have, denoting by r the radius vector from the center and by r_0 the radius of the cell:
For $r = r_0$:

$$D_{i1}\frac{\partial c_{i1}}{\partial r} = -h_1(c_{i1} - c_{e1}) = D_{e1}\frac{\partial c_{e1}}{\partial r}; \qquad D_{i2}\frac{\partial c_{i2}}{\partial r} = -h_2(c_{i2} - c_{e2}) = D_{e2}\frac{\partial c_{e2}}{\partial r}. \tag{4}$$

We shall now reduce the system (2) to a simple partial differential equation of second order in t.

The second equation of (2) gives:

$$c_{i1} = \frac{1}{a_{21}}\frac{\partial c_{i2}}{\partial t} - \frac{D_{i2}}{a_{21}}\nabla^2 c_{i2} - \frac{a_{22}}{a_{21}}c_{i2}. \tag{5}$$

Differentiating with respect to t, we find

$$\frac{\partial c_{i1}}{\partial t} = \frac{1}{a_{21}}\frac{\partial^2 c_{i2}}{\partial t^2} - \frac{D_{i2}}{a_{21}}\frac{\partial}{\partial t}\nabla^2 c_{i2} - \frac{a_{22}}{a_{21}}\frac{\partial c_{i2}}{\partial t}. \tag{6}$$

Introducing equations (5) and (6) into the first equation of the system (2), putting

$$\nabla^4 c_{i2} = \nabla^2\nabla^2 c_{i2} = \frac{\partial^4 c_{i2}}{\partial x^4} + \frac{\partial^4 c_{i2}}{\partial y^4} + \frac{\partial^4 c_{i2}}{\partial z^4} + 2\frac{\partial^4 c_{i2}}{\partial x^2 \partial y^2} + 2\frac{\partial^4 c_{i2}}{\partial x^2 \partial z^2} + 2\frac{\partial^4 c_{i2}}{\partial y^2 \partial z^2}, \tag{7}$$

and rearranging, we find:

$$\frac{\partial^2 c_{i2}}{\partial t^2} - (a_{11} + a_{22}) \frac{\partial c_{i2}}{\partial t} - (D_{i1} + D_{i2}) \frac{\partial}{\partial t} \nabla^2 c_{i2} + D_{i1} D_{i2} \nabla^4 c_{i2} + (a_{22} D_{i1} + a_{11} D_{i2}) \nabla^2 c_{i2} + (a_{11} a_{22} - a_{12} a_{21}) c_{i2} = 0 . \tag{8}$$

Solving the first equation of the system (2) for c_{i2}, differentiating, and introducing into the second equation of the system (2), we find in a similar way

$$\frac{\partial^2 c_{i1}}{\partial t^2} - (a_{11} + a_{22}) \frac{\partial c_{i1}}{\partial t} - (D_{i1} + D_{i2}) \frac{\partial}{\partial t} \nabla^2 c_{i1} + D_{i1} D_{i2} \nabla^4 c_{i1} + (a_{11} D_{i2} + a_{22} D_{i1}) \nabla^2 c_{i1} + (a_{11} a_{22} - a_{12} a_{21}) c_{i1} = 0 . \tag{9}$$

Subtracting equation (8) from equation (9) and putting

$$c_{i1} - c_{i2} = \Phi_i , \tag{10}$$

we obtain:

$$\frac{\partial^2 \Phi_i}{\partial t^2} - (a_{11} + a_{22}) \frac{\partial \Phi_i}{\partial t} - (D_{i1} + D_{i2}) \frac{\partial}{\partial t} \nabla^2 \Phi_i + D_{i1} D_{i2} \nabla^4 \Phi_i + (a_{11} D_{i2} + a_{22} D_{i1}) \nabla^2 \Phi_i + (a_{11} a_{22} - a_{12} a_{21}) \Phi_i = 0 . \tag{11}$$

System (3) differs from system (2) essentially only in that the coefficients a_{11}, a_{12}, a_{21}, and a_{22} vanish.

Therefore, putting

$$\Phi_e = c_{e1} - c_{e2} , \tag{12}$$

we see that the system (3) is equivalent to

$$\frac{\partial^2 \Phi_e}{\partial t^2} - (D_{e1} + D_{e2}) \frac{\partial}{\partial t} \nabla^2 \Phi_e + D_{e1} D_{e2} \nabla^4 \Phi_e = 0. \tag{13}$$

This can also be shown directly.

Put

$$u = c_{e1} + c_{e2} , \tag{14}$$

so that

$$c_{e1} = \frac{u + \Phi_e}{2}; \quad c_{e2} = \frac{u - \Phi_e}{2}. \tag{15}$$

Introducing this into (3), we find:

$$\frac{\partial u}{\partial t} + \frac{\partial \Phi_e}{\partial t} = D_{e1}\nabla^2 u + D_{e1}\nabla^2 \Phi_e; \tag{16}$$

$$\frac{\partial u}{\partial t} - \frac{\partial \Phi_e}{\partial t} = D_{e2}\nabla^2 u - D_{e2}\nabla^2 \Phi_e. \tag{17}$$

Subtracting (17) from (16) we have

$$2\frac{\partial \Phi_e}{\partial t} = (D_{e1} - D_{e2})\nabla^2 u + (D_{e1} + D_{e2})\nabla^2 \Phi_e. \tag{18}$$

From equation (18) we have:

$$\nabla^2 u = \frac{2}{D_{e1} - D_{e2}}\frac{\partial \Phi_e}{\partial t} - \frac{D_{e1} + D_{e2}}{D_{e1} - D_{e2}}\nabla^2 \Phi_e; \tag{19}$$

or,

$$\frac{\partial}{\partial t}\nabla^2 u = \frac{2}{D_{e1} - D_{e2}}\frac{\partial^2 \Phi_e}{\partial t^2} - \frac{D_{e1} + D_{e2}}{D_{e1} - D_{e2}}\frac{\partial}{\partial t}\nabla^2 \Phi_e. \tag{20}$$

Applying the Laplacian operator to both sides of equation (16) we have

$$\frac{\partial}{\partial t}\nabla^2 u + \frac{\partial}{\partial t}\nabla^2 \Phi_e = D_{e1}\nabla^4 u + D_{e1}\nabla^4 \Phi_e. \tag{21}$$

Similarly, from equation (19) we have

$$\nabla^4 u = \frac{2}{D_{e1} - D_{e2}}\frac{\partial}{\partial t}\nabla^2 \Phi_e - \frac{D_{e1} + D_{e2}}{D_{e1} - D_{e2}}\nabla^4 \Phi_e. \tag{22}$$

Introducing equations (20) and (22) into equation (21) we obtain equation (13).

In order to obtain the boundary conditions for the systems (11) and (13) it seems to be necessary to make the same restrictive, though not implausible, assumption as made by A. Weinberg, namely, we put

$$\frac{h_1}{D_{i1}} = \frac{h_2}{D_{i2}} = k_1; \quad \frac{D_{e1}}{D_{i1}} = \frac{D_{e2}}{D_{i2}} = k_2. \tag{23}$$

In that case we obtain from equations (4):
For $r = r_0$:

$$\frac{\partial \Phi_i}{\partial r} + k_1 \Phi_i = k_1 \Phi_e; \tag{24}$$

$$\frac{\partial \Phi_i}{\partial r} = k_2 \frac{\partial \Phi_e}{\partial r}. \tag{25}$$

Any solution Φ_{0i} of the equation

$$D_{i1}D_{i2}\nabla^4\Phi + (a_{11}D_{i2} + a_{22}D_{i1})\nabla^2\Phi + (a_{11}a_{22} - a_{12}a_{21})\Phi = 0 \tag{26}$$

is also a solution of equation (11).

Hence the solution of equation (11) may be put in the form

$$\Phi_i = \Phi_i^* + \Phi_{0i} \tag{27}$$

where Φ_{0i} is independent of time, while Φ_i^* depends on it and satisfy the general equation (11).

Putting

$$\Phi_i^* = \psi_i e^{\nu t}, \tag{28}$$

where ψ_i is a function of the space coordinates only, introducing this into equation (11), and putting

$$\frac{a_{11}D_{i2} + a_{22}D_{i1} - (D_{i1} + D_{i2})\nu}{D_{i1}D_{i2}} = \alpha_1; \tag{29}$$

$$\frac{\nu^2 - (a_{11} + a_{22})\nu + a_{11}a_{22} - a_{12}a_{21}}{D_{i1}D_{i2}} = \alpha_2; \tag{30}$$

we find

$$\nabla^4\psi_i + \alpha_1\nabla^2\psi_i + \alpha_2\psi_i = 0. \tag{31}$$

Consider the equation

$$\nabla^2\psi_i \pm \lambda^2\psi_i = 0, \tag{32}$$

where λ is a constant.

From that equation, we have

$$\nabla^4\psi_i \pm \lambda^2\nabla^2\psi_i = 0. \tag{33}$$

Put

$$\lambda^2 = \lambda' + \lambda''. \tag{34}$$

Then

$$\nabla^4\psi_i \pm (\lambda' + \lambda'')\nabla^2\psi_i = 0 \tag{35}$$

or,

$$\nabla^4\psi_i \pm \lambda'\nabla^2\psi_i \pm \lambda''\nabla^2\psi_i = 0. \tag{36}$$

Substituting equation (32) into the last term of the left-hand side of equation (36), we find:

$$\nabla^4\psi_i \pm \lambda'\nabla^2\psi_i - \lambda''\lambda^2\psi_i = 0. \tag{37}$$

Put

$$\lambda' = \alpha_1. \tag{38}$$

Hence, because of equation (34)

$$\lambda'' = \lambda^2 - \alpha_1 . \tag{39}$$

Introducing (38) and (39) into (37) we find

$$\nabla^4\psi_i \pm \alpha_1\nabla^2\psi_i - (\lambda^2 - \alpha_1)\lambda^2\psi_i = 0 . \tag{40}$$

Equation (40) becomes identical with equation (31) if we make

$$(\lambda^2 - \alpha_1)\lambda^2 = -\alpha_2 . \tag{41}$$

Since the plus sign appears before α_1 in equation (31), any solution of the equation

$$\nabla^2\psi_i + \lambda^2\psi_i = 0 , \tag{42}$$

where λ^2 is expressed in terms of α_1 and α_2 through equation (41), is also a solution of equation (31).

When we try to satisfy the boundary conditions, we shall find that this can be done only if λ^2 has certain discrete values which are the eigenvalues of the boundary problem. In general, for each eigenvalue of λ^2 we obtain a pair of values of ν in equation (28). This is seen in the following way.

Equation (41) may be written:

$$\lambda^4 - \alpha_1\lambda^2 + \alpha_2 = 0 , \tag{43}$$

and its roots are

$$\lambda^2 = \frac{\alpha_1}{2} \pm \frac{1}{2}\sqrt{\alpha_1^2 - 4\alpha_2} . \tag{44}$$

Introducing into equation (44) the expressions (29) and (30) we find after laborious rearrangements the following quadratic equation for ν:

$$\begin{aligned} \nu^2 + [\lambda^2(D_{i1} + D_{i2}) - a_{11} - a_{22}]\,\nu + \lambda^4 D_{i1}D_{i2} \\ - \lambda^2(a_{11}D_{i2} + a_{22}D_{i1}) + a_{11}a_{22} - a_{12}a_{21} = 0 . \end{aligned} \tag{45}$$

In general ν will be complex, and expression (28) will thus represent a damped oscillation. The real part of ν is zero only for a particular value of λ^2, which makes the coefficient of ν in (45) vanish. Unless this value happens to be an eigenvalue, we thus see that all oscillations are damped. For some values of λ^2 the damping may be negative, which means that for the vibrational configuration corresponding to that value of λ^2 the whole system becomes unstable.

Similar considerations may be applied to equation (13), by first putting

$$\Phi_e = \Phi_{0e} + \Phi_e^* , \tag{46}$$

and then putting

$$\Phi_e^* = \psi_e e^{\bar{\nu} t} . \tag{47}$$

This leads to the equation

$$\nabla^4 \psi_e + \bar{\alpha}_1 \nabla^2 \psi_e + \bar{\alpha}_2 \psi_e = 0 \tag{48}$$

with

$$\bar{\alpha}_1 = -\frac{D_{e1} + D_{e2}}{D_{e1} D_{e2}} \nu ; \quad \bar{\alpha}_2 = \frac{\bar{\nu}^2}{D_{e1} D_{e2}} . \tag{49}$$

Equation (48) is equivalent to

$$\nabla^4 \psi_e + \bar{\lambda}^2 \psi_e = 0 \tag{50}$$

with

$$\bar{\lambda}^2 = \frac{\bar{\alpha}_1}{2} \pm \frac{1}{2} \sqrt{\bar{\alpha}_1^2 - 4\bar{\alpha}_2} . \tag{51}$$

A solution of equation (42) in polar coordinates is given by (Schmidt, 1934):

$$\psi_i'(r, \phi, \theta) = \sum_m \frac{1}{\sqrt{r}} J_{m+\frac{1}{2}}(\lambda r) \sum_{n=0}^{n=m} \Big\{ a_n^{(m)} \cos(n\phi) + b_n^{(m)} \sin(n\phi) \Big\} P_m^{(n)}(\cos\theta) , \tag{52}$$

where $J_{m+\frac{1}{2}}$ denotes the Bessel function of order $m + \frac{1}{2}$, $P_m^{(n)}$ is the nth derivative of the Legeandre polynomial of order m; $a_n^{(m)}$, $b_n^{(m)}$, are coefficients.

Therefore, a solution of equation (11) is given by:

$$\Phi_i'(r, \phi, \theta, t) = \sum_m \frac{1}{\sqrt{r}} J_{m+\frac{1}{2}}(\lambda r) \sum_{n=0}^{n=m} \Big\{ a_n^{(m)} \cos(n\phi) + b_n^{(m)} \sin(n\phi) \Big\} P_m^{(n)}(\cos\theta) \left[C_m^{(1)} e^{\nu_1(\lambda) t} + C_m^{(2)} e^{\nu_2(\lambda) t} \right] , \tag{53}$$

where $\nu_1(\lambda)$ and $\nu_2(\lambda)$ are the two roots of equation (45) and $C_{m\nu_1}$ and $C_{m\nu_2}$ are coefficients.

Similarly, equation (13) for Φ_e is solved by

$$\Phi_e'(r,\phi,\theta,t) = \sum_m \frac{1}{\sqrt{r}} J_{m+\frac{1}{2}}(\bar{\lambda}r) \sum_{n=0}^{n=m} \left\{ \bar{a}_n^{(m)} \cos(n\phi) + \bar{b}_n^{(m)} \sin(n\phi) \right\} P_m^{(n)}(\cos\theta) \tag{54}$$

$$[\bar{C}_m^{(1)} e^{\bar{\nu}_1(\bar{\lambda})t} + \bar{C}_m^{(2)} e^{\bar{\nu}_2(\bar{\lambda})t}] .$$

The functions Φ_i and Φ_e must satisfy the boundary conditions (24) and (25).

It can be readily seen by putting $a_{11} = a_{22} = a_{12} = a_{21} = 0$ in equation (45) that for any real value of $\bar{\lambda}$, the quantity $\bar{\nu}$ is real. If all the constants in equation (45) are so chosen that the same thing holds about ν, then we can use the following device.

Denote

$$T_m(\lambda;r) = \frac{d}{dr}\left[\frac{1}{\sqrt{r}} J_{m+\frac{1}{2}}(\lambda r) \right] . \tag{55}$$

Let $\nu_1(\lambda)$ be the root of equation (45) which corresponds to the minus sign before the radical in the solution of that equation; (the *smaller* root, if they are real). Let $\nu_2(\lambda)$ be the other root. Let $\bar{\nu}_1(\bar{\lambda})$ and $\bar{\nu}_2(\bar{\lambda})$ have the same meaning for the two roots which are associated with equation (48). Consider first the particular case of (53) and (54) where $C_m^{(2)} = \bar{C}_m^{(2)} = 0$.

Let

$$\bar{\nu}_1(\bar{\lambda}) = \nu_1(\lambda) . \tag{56}$$

This establishes a relation between $\bar{\lambda}$ and λ, so that the former becomes a function $f_1(\lambda)$ of the latter:

$$\bar{\lambda} = f_1(\lambda) . \tag{57}$$

Consider the values of $J_{m+\frac{1}{2}}(\bar{\lambda}r)$ and $T_m(\bar{\lambda},r)$. We have

$$J_{m+\frac{1}{2}}(\bar{\lambda},r) = J_{m+\frac{1}{2}}[f_1(\lambda)r] = U_m(\lambda,r) ; \tag{58}$$

$$T_m(\bar{\lambda},r) = T_m[f_1(\lambda)r] = V_m(\lambda,r) . \tag{59}$$

Substituting this into equation (54), we find, because of (56):

$$\Phi_e'(r,\phi,\theta,t) = \sum_m \frac{1}{\sqrt{r}} U_m(\lambda,r) \sum_{n=0}^{n=m} \left\{ \bar{a}_n^{(m)} \cos(n\phi) + \bar{b}_n^{(m)} \sin(n\phi) \right\} P_m^{(n)}(\cos\theta)\, C_m^{(1)} e^{\nu_1(\lambda)t} . \tag{60}$$

Introducing expressions (53) and (60) into the boundary conditions (24) and (25), and equating the coefficients of identical terms in ϕ, and θ, we find:

$$\left[T_m(\lambda, r_0) + \frac{k_1}{\sqrt{r_0}} J_{m+\frac{1}{2}}(\lambda, r_0) \right] a_n^{(m)} = \left[\frac{k_1}{\sqrt{r_0}} U_m(\lambda, r_0) \right] \bar{a}_n^{(m)} \tag{61}$$

and

$$[T_m(\lambda, r_0)]\, a_n^{(m)} = [k_2 V_m(\lambda, r_0)]\, \bar{a}_n^{(m)} . \tag{62}$$

Similar relations hold for $b_n^{(m)}$ and $\bar{b}_n^{(m)}$.

If equations (61) and (62) hold for any values of $a_n^{(m)}$ and $\bar{a}_n^{(m)}$, then we must have

$$\left[T_m(\lambda, r_0) + \frac{k_1}{\sqrt{r_0}} J_{m+\frac{1}{2}}(\lambda, r_0) \right] k_2 V_m(\lambda, r_0) = \frac{k_1}{\sqrt{r_0}} T_m(\lambda, r_0)\, U_m(\lambda, r_0) . \tag{63}$$

The roots of the transcendental equation (63) are the *eigenvalues* $\lambda_m^{(\mu)}$ $(m = 1, 2, 3 \cdots;\ \mu = 1, 2, 3 \cdots)$ of our boundary problem. These values satisfy conditions (61) and (62). But then the ratio $b_n^{(m)}/\bar{b}_n^{m}$ becomes fixed and thus either only the $b_n^{(m)}$'s or the $b_n^{(m)}$'s can be chosen freely. Putting

$$\bar{b}_n^{(m)} = \gamma_m b_n^{(m)} , \tag{64}$$

we now have a particular solution of equations (11) and (13), satisfying the boundary conditions (24) and (25):

$$\Phi_i''(r, \phi, \theta, t) = \sum_{m=0}^{\infty} \sum_{\mu=1}^{\infty} \frac{1}{\sqrt{r}} J_{m+\frac{1}{2}}(\lambda_m^{(\mu)} r) \sum_{n=0}^{m} \left\{ a_n^{(m)} \cos(n\phi) + b_n^{(m)} \sin(n\phi) \right\} P_m^{(n)}(\cos\theta)\, C_m^{(1)}\, e^{\nu_1(m,\mu)\, t} , \tag{65}$$

and

$$\Phi_e''(r, \phi, \theta, t) = \sum_{m=0}^{\infty} \sum_{\mu=1}^{\infty} \frac{1}{\sqrt{r}} U(\lambda_m^{(\mu)}, r) \sum_{n=0}^{m} \left\{ \bar{a}_n^{(m)} \cos(n\phi) + \gamma_m b_n^{(m)} \sin(n\phi) \right\} P_m^{(n)}(\cos\theta)\, C_m^{(1)}\, e^{\nu_1(m,\mu)\, t} . \tag{66}$$

It must be remarked that although from a mathematical point of view the summations in equations (65) may be extended over all values of m from 0 to ∞, nevertheless from physical considerations the value $m = 1$ should be omitted. The reason for this is that the derivative of $J_{3/2}(r)$ is not equal to zero at $r = 0$. But in the absence of any point sources at the center, the derivative of Φ_i must be continuous at $r = 0$. This remark holds also for the subsequent equation (72). It does *not* apply, however, to (66) and (73), since in both of these $r > r_0$.

Now consider the case where $C_m^{(1)} = \bar{C}_m^{(1)} = 0$ in equations (53) and (54). Let

$$\bar{\nu}_2(\bar{\lambda}) = \nu_2(\lambda) . \tag{67}$$

This establishes a relation

$$\bar{\lambda} = f_2(\lambda) , \tag{68}$$

which is, in general, different from relation (56).
We now put

$$J_{m+\frac{1}{2}}(\lambda r) = J_{m+\frac{1}{2}}[f_2(\lambda) r] = \bar{U}_m(\lambda, r_0) ; \tag{69}$$

$$T_m(\bar{\lambda}, r) = T_m[f_2(\lambda), r] = \bar{V}_m(\lambda, r) . \tag{70}$$

By a similar argument as before we now find that the boundary conditions (24) and (25) are satisfied by (53) and (54) if

$$\left[T_m(\lambda, r_0) + \frac{k_1}{\sqrt{r_0}} J_{m+\frac{1}{2}}(\lambda r_0) \right] k_2 \bar{V}_m(\lambda, r_0) = \frac{k_1}{\sqrt{r_0}} T_m(\lambda, r_0) \bar{U}_m(\lambda, r_0) . \tag{71}$$

This equation gives another set $\lambda_m^{(\eta)}$ of *eigenvalues*, and we obtain as another particular solution of equations (11) and (13):

$$\Phi_i(r, \phi, \theta, t) = \sum_{m=0}^{\infty} \sum_{\eta=1}^{\infty} \frac{1}{\sqrt{r}} J_{m+\frac{1}{2}}(\lambda_m^{(\eta)} r) \sum_{n=0}^{m} \left\{ a_n^{(m)} \cos(n\phi) + b_n^{(m)} \sin(n\phi) \right\} P_m^{(n)}(\cos\theta) C_m^{(2)} e^{\nu_2(m,\eta)t} ; \tag{72}$$

and

$$\Phi_e(r, \phi, \theta, t) = \sum_{m=0}^{\infty} \sum_{\eta=1}^{\infty} \frac{1}{\sqrt{r}} \bar{U}(\lambda_m^{(n)}, r) \sum_{n=0}^{m} \left\{ \bar{a}_n^{(m)} \cos(n\phi) + \bar{\gamma}_m b_n^{(m)} \sin(n\phi) \right\} P_m^{(n)}(\cos\theta) C_m^{(2)} e^{\nu_2(m,\eta)t} ; \tag{73}$$

with $\bar{\gamma}_m$ different from γ_m, which appears in (63) and (66).

The sum of (65) and (72) and the sum of (66) and (73) form also a solution of equations (11) and (13).

A particular solution of equation (13) is also obtained if in expression (54) for Φ_e we substitute $J_{-m-\frac{1}{2}}(\bar{\lambda} r)$ for $J_{m+\frac{1}{2}}(\bar{\lambda} r)$. We may satisfy the boundary conditions in the same way and obtain a solution of $\Phi_i'''(r, \phi, \theta, t)$ and $\Phi_e'''(r, \phi, \theta, t)$. The functions

$$\begin{aligned} \Phi_i^* &= A_1\Phi_i + A_2\Phi_i'' + A_3\Phi_i''''; \\ \Phi_e^* &= A_1\Phi_e + A_2\Phi_e'' + A_3\Phi_e'''' \end{aligned} \tag{74}$$

where A_1, A_2, and A_3 are arbitrary constants, Φ_i and Φ_e are given by (72) and (73); and Φ_i'' and Φ_e'' are given by (65) and (66); are again solutions of (11) and (13).

The functions Φ_i^* and Φ_e^* are oscillating with respect to the variables r, ϕ, and θ, and assume in some regions negative values. The circumstance that Φ_i^* and Φ_e^* become negative does not necessarily imply that either of the quantities c_{i1}, c_{i2}, c_{e1}, or c_{e2} become negative. In general, however, this may happen to be the case.

The complete solutions of equations (11) and (13) are, however, given by expressions (27) and (46). As long as the amplitudes of the oscillations of Φ_i^* and Φ_e^* are less than the smallest values of Φ_{0i} or Φ_{0e} in the corresponding region, the complete solution has physical meaning. The above requirement puts certain restrictions on the coefficients A_1, A_2, and A_3 in expressions (74). This is analogous to the requirement expressed by relations (22) of chapter vi of the author's book (Rashevsky, 1938, 1948).

If, however, some values of ν, as given by equation (45) are complex, the above procedure cannot be used because we now cannot satisfy (56). Whether we still can satisfy in general the boundary conditions (24) and (25) in that case is a question which we do not attempt to answer here. Those boundary conditions may, however, be satisfied for the special case $D_{e1} = D_{e2} = \infty$; $\Phi_e = 0$. Introducing for this case (53) into (24) we find

$$\frac{d}{dr}\left[\frac{1}{\sqrt{r}} J_{m+\frac{1}{2}}(\lambda r)\right]_{r=r_0} + \frac{k_1}{\sqrt{r_0}} J_{m+\frac{1}{2}}(\lambda r_0) = 0$$

as the equation which determines the eigenvalues. Then by a similar procedure as above we can obtain a solution Φ_i^* which oscillates with respect to time also. It gives periodic oscillations inside of the cell. As we have seen, however, these oscillations are, in general, damped.

Let us now investigate the solutions of Φ_{0i} and Φ_{0e} which do not depend on time.

Putting

$$\frac{a_{11}D_{i2} + a_{22}D_{i1}}{D_{i1}D_{i2}} = \beta_1; \quad \frac{a_{11}a_{22} - a_{12}a_{21}}{D_{i1}D_{i2}} = \beta_2, \tag{75}$$

we reduce equation (26) to the form

$$\nabla^4\Phi + \beta_1\nabla^2\Phi + \beta_2\Phi = 0. \tag{76}$$

According to what was said above, any solution of the equation

$$\nabla^2\Phi + \kappa^2\Phi = 0, \tag{77}$$

where

$$\kappa^2 = \frac{\beta_1}{2} \pm \frac{1}{2}\sqrt{\beta_1^2 - 4\beta_2} \tag{78}$$

is a solution of (76).

Equation (77) is of the same form as equation (42). There is, however, a great difference between the two. Whereas the parameter λ^2 in equation (42) is variable, and is determined by the requirements at the boundary, the parameter κ^2 in equation (77) is a fixed physical constant.

The solution Φ_{0e} satisfies the equation which is obtained from (13) by making all derivations with respect to t zero. Thus Φ_{0e} is the solution of

$$\nabla^4\Phi = 0, \tag{79}$$

which has the same solution as

$$\nabla^2\Phi = 0. \tag{80}$$

The general expression for such a solution of (80) which at infinity tends to a constant value $\Phi_0 = c_{01} - c_{02}$ is given in polar coordinates by

$$\Phi_{0e}(r, \phi, \theta) = \Phi_0 + \sum_{n=0}^{\infty} r^{-m-1}\Big\{ p_n^{(m)} \cos(n\phi) + q_n^{(m)} \sin(n\phi)\Big\} P_m^{(n)}(\cos\theta), \tag{81}$$

where $p_n^{(m)}$ and $q_n^{(m)}$ are coefficients.

If both values of κ^2, as given by equation (78), are positive, then for each value we may still satisfy equation (77) by an expression of the form of (52). Introducing this and (81) into the boundary conditions (24) and (25), and again equating term by term we come to the relations

$$\left[T_m(\kappa, r_0) + \frac{k_1}{\sqrt{r_0}} J_{m+\frac{1}{2}}(\kappa, r_0) \right] a_n^{(m)} = k_1 p_n^{(m)} r_0^{-m-1} \tag{82}$$

and

$$[T_m(\kappa, r_0)]\, a_n^{(m)} = -k_2(m+1) r_0^{-m-2} p_n^{(m)} . \tag{83}$$

The above two relations require

$$\begin{aligned} &-k_2(m+1) r_0^{-m-2} \left[T_m(\kappa, r_0) + \frac{k_1}{\sqrt{r_0}} J_{m+\frac{1}{2}}(\kappa, r_0) \right] \\ &= k_1 r_0^{-m-1} T_m(\kappa, r_0). \end{aligned} \tag{84}$$

But this relation is, in general, not satisfied for any κ. Hence the only term for which the boundary conditions (24) and (25) can be satisfied is one that does not contain either ϕ or θ. The problem reduces to the one discussed in detail elsewhere (Rashevsky, 1938; 1948, chap. iv). As has been shown there a solution which is always positive exists, as long as r_0 does not exceed a critical value r_0^*. Since there are two values of κ, there are *two* such solutions.

Formally the same procedure may be applied for $\kappa^2 < 0$. In that case the Bessel functions have an imaginary argument. Again we find that only the centrally symmetric solution, represented by $J_{\frac{1}{2}}(\kappa, r)$ satisfies the boundary conditions. For an imaginary argument this term reduces to $(\sinh \kappa r)/r$ multiplied by a complex coefficient. Since $AJ_{\frac{1}{2}}(\kappa r)$, where A is any real or complex number; also satisfies the differential equation which is satisfied by $J_{\frac{1}{2}}(\kappa r)$, therefore, by a proper choice of a complex A the solution may be put into the form $B(\sinh \kappa r)/r$, where B is real. This reduces again to the case studied previously (Rashevsky, 1938; 1948, chap. iv).

It may, however, happen that equation (78) has two conjugate complex roots, so that

$$\kappa^2 = (a + bi)^2 . \tag{85}$$

Again we have to consider only centrally symmetric solutions. The case is best studied by transforming equation (76) into polar coordinates, and omitting all terms containing derivatives with respect to ϕ and θ.

If we make this transformation and introduce a new variable

$$u = \Phi r , \tag{86}$$

equation (76) becomes:

$$\frac{d^4u}{dr^4} + \beta_1 \frac{d^2u}{dr^2} + \beta_2 u = 0. \tag{87}$$

As we have seen, any solution of

$$\frac{d^2u}{dr^2} = \kappa^2 u = 0, \tag{88}$$

where κ^2 is given by (78), is also a solution of (87).

The general solution of (88) is

$$u = A \sin \kappa r + B \cos \kappa r. \tag{89}$$

Whether κ is real or complex, $B = 0$, because $\Phi = u/r$ must be finite for $r = 0$. When κ^2 is given by equation (85), we have

$$\begin{aligned} \sin \kappa r = \sin ar \cos ibr + \cos ar \sin ibr = \sin ar \cosh br \\ + i \cos ar \sinh br. \end{aligned} \tag{90}$$

This complex expression which satisfies (88) has no physical meaning. The real and imaginary parts taken separately do not satisfy (88). It can, however, be shown that they satisfy equation (87). Substituting sin ar cosh br into (87) we find:

$$\begin{aligned} [a^4 + b^4 - 6a^2b^2 + \beta_1(b^2 - a^2) + \beta_2] \sin ax \cosh bx \\ + [4ab(b^2 - a^2) + 2\beta_1 ab] \cos ax \sinh bx = 0. \end{aligned} \tag{91}$$

If (91) is to hold for any value of x, both expressions in brackets must vanish.

The requirement that the second expression in brackets must vanish leads to

$$\beta_1 = 2(a^2 - b^2). \tag{92}$$

The same requirement for the first expression, combined with (92), leads to

$$16a^2b^2 = 4\beta_2 - \beta_1^2. \tag{93}$$

If, however, κ^2 is given by (78) and is of the form (85), then we have, by equating the real and imaginary parts:

$$a^2 - b^2 = \frac{\beta_1}{2}; \quad 4ab = \sqrt{4\beta_2 - \beta_1^2}. \tag{94}$$

Equations (94) lead directly to (92) and (93).

Since sin ar cosh br + i cos ar sinh br satisfies (87) and, as we just have seen, sin ar cosh br does satisfy it, therefore, cos ar sinh br

also satisfies (87). Hence the centrally symmetric solution in this case is given by

$$\Phi_{0i} = A \frac{\sin ar \cosh br}{r} + B \frac{\cos ar \sinh br}{r}, \qquad (95)$$

where a and b are determined in terms of β_1 and β_2 by equations (94). The solution for the outside medium, Φ_{0e}, is of the form $A_1/r + B_1$. The coefficients A, B, A_1, and B_1 are again determined as before (Rashevsky, 1938; 1948, chap. iv).

The time dependent oscillating solutions, which are in general highly symmetric, are thus superimposed upon a centrally symmetric solution. The resulting distribution of concentrations is again asymmetric. Most complex structures may thus be obtained. However, since in general *all* oscillations are damped, the only configuration which may last indefinitely is the centrally symmetric one. If the damping for some of the oscillations is very small, the asymmetric distributions of concentrations which correspond to those oscillations may persist for an appreciable time.

The following remark is noteworthy. If we make $a_{11} = a_{22} = 0$ and $a_{12} = -a_{21}$, in equations (1) the reactions, *in the absence of any diffusion,* are described by the system

$$\frac{dc_1}{dt} = a_{12}c_2; \quad \frac{dc_2}{dt} = -a_{12}c_1. \qquad (96)$$

This system (96) has an *undamped* periodic solution with the frequency a_{12}. Yet even with $a_{11} = a_{22} = 0$; $a_{12} = -a_{21}$, all oscillations of the general solution of the diffusion equation are again damped. This seems to indicate that the damping is caused largely by the process of diffusion itself. It would make somewhat unlikely the possibility that the introduction of *non-linear* reaction equations, which may have periodic solutions that are *always* undamped (Lotka, 1925; Volterra, 1931; Morales, 1944), may lead to undamped oscillations in the solution of the general diffusion problem and thus lead to permanent stable but highly complex configurations within the cell.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 10, 1948

THE KINETICS OF BLOOD COAGULATION

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The kinetics of the blood coagulation system have been formulated and an expression obtained for the "prothrombin time" in terms of the concentrations of the components of the system. A linear plot of data obtained from plasma dilution curves gives the values of the parameters of the system, and yields a mathematical method of comparing relative thromboplastin potencies. The analytical expressions given lead to the proper choice of thromboplastin potency and plasma dilution for minimum error in the clinical determination of prothrombin.

In spite of the many theories which have at one time been in vogue, it is generally agreed today that the coagulation of blood occurs in two distinct, consecutive phases, viz., 1: The formation of thrombin, (T), from prothrombin, (P), and 2: The conversion of fibrinogen, (F), to fibrin under the influence of thrombin. It is also generally agreed that ionic calcium must be present in the system.

The exact role of calcium, and the mechanism of the first phase, have been the subject of much controversy and confusion. Early observers held to the idea that calcium alone, or calcium and thromboplastin, (Th), combined with prothrombin to form thrombin. With the isolation of prothrombin and thrombin in relatively pure states, it has become clear that these concepts are no longer tenable. J. Mellanby (1939), H. Eagle (1935), and others have shown that prothrombin gives rise to thrombin only in the presence of both calcium and thromboplastin. The amount of thrombin formed is independent of the amount of thromboplastin in the system, but directly proportional to the initial amount of prothrombin. H. Eagle has submitted evidence that thromboplastin is a lipoprotein and that this agent *together* with calcium constitutes an enzyme which catalyzes the conversion of prothrombin to thrombin.

There has been less controversy regarding the second phase of the clotting process. The evidence appears to indicate decisively that thrombin is an enzyme which converts the soluble protein, fibrinogen, into the insoluble form, fibrin. More recent work of J. Ferry et al (1947) supports the view that the process is a polymerization. It now

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appears certain that the reaction is not proteolytic, as it was once thought, but there can be no logical objection to the concept that the role of thrombin is enzymatic.

In view of the foregoing briefly reviewed evidence and respective of J. Mellanby's study (1939) of the thromboplastin–calcium equilibrium, we may with some confidence list the following points which constitute the qualitative basis upon which any adequate formulation of the kinetics of the process must rest:

1. Calcium and thromboplastin form an active complex which is an enzyme and acts upon prothrombin with the resultant formation of thrombin.
2. The affinity of thromboplastin for calcium is great, but the combination is dissociable in the equilibrium sense.
3. Once formed from prothrombin, thrombin catalytically converts fibrinogen to fibrin.
4. The conversion of prothrombin to thrombin by the thromboplastin–calcium complex and the conversion of fibrinogen to fibrin by thrombin exhibit all the known properties of enzymatic reactions.

It is pointed out here that the present scheme of blood coagulation is incomplete in the sense that it does not include those factors controlling the fluidity of blood *in vivo*. Also the multiplicity of factors which have thromboplastic activity cause one to doubt the validity of the point of view that thromboplastin is an entity. Finally, the work on "Ac–globulin" (Ware, 1947) may lead to some revision of the now accepted concept of prothrombin activities. However, the foregoing scheme is a fairly complete description of the sequence of events, particularly as they occur *in vitro* in the clinical determination of prothrombin.

The determination of prothrombin has steadily increased in importance in clinical medicine, especially in dicumarol therapy. Accurate and consistent results are imperative and must finally be based on an understanding of the rate process. Indeed, the view has been expressed that if accurate prothrombin determinations are not available, dicumarol therapy must be discarded. (Martin, 1947). The employment of enzyme systems in clinical determinations is a common procedure. Thus far, however, the determination of prothrombin by the "one stage" method has remained in an empirical and somewhat unsatisfactory state. It remains for this system to be treated in a quantitative manner and for the rate of the over-all process to be formulated on the basis of present information regarding the constituents of the system. It is the purpose of this paper to present

such a kinetic formulation, to examine the features of the resulting expression, and to compare the results of the mathematical treatment with experimental data.

The series of reactions to be considered are as follows:

$$\begin{aligned} Th + Ca^{++} &\underset{\rightarrow}{\leftarrow} Th' \\ Th' + P &\underset{\rightarrow}{\leftarrow} Th' \cdot P \\ Th' \cdot P &\underset{\rightarrow}{\leftarrow} Th' + T \\ T + F &\underset{\rightarrow}{\leftarrow} T \cdot F \\ T \cdot F &\rightarrow T \cdot (\text{fibrin}). \end{aligned} \tag{1}$$

The mathematical description of this type of system involves great difficulty unless certain assumptions may be made. In fact, the exact solution is available only when each reaction is first (or pseudo-first) order. One stipulation which frequently can be made with a high degree of precision is that the entire system should be in the steady state. This assumption is particularly applicable to consecutive enzyme reactions, and when it can be made, a very powerful method is available in the form of the Christiansen formulation. (See Hammett, 1940). To exhibit the method let us consider the generalized case

$$\begin{aligned} A + B &\underset{k_1}{\overset{k_{-1}}{\leftarrow}} X_1 + C \\ D + X_1 &\underset{k_2}{\overset{k_{-2}}{\leftarrow}} X_2 + E \\ &\vdots \qquad\qquad \vdots \\ L + X_{n-1} &\underset{k_n}{\overset{k_{-n}}{\leftarrow}} M + N. \end{aligned} \tag{2}$$

Here the X_i are unstable intermediates and are assumed to be in a steady state, i.e., the rate at which X_i is produced in step i is equal to the rate at which it is consumed in the subsequent step. If the system is in the steady state, the net rates of all the steps are equal and are in turn equal to the over-all rate, V, of conversion of A and B to the final products M and N. Thus

$$v_1 - v_{-1} = v_2 - v_{-2} = \cdots v_n - v_{-n} = V, \tag{3}$$

and

$$\begin{aligned} V &= w_1 - w_{-1}(X_1) = w_2(X_1) - w_{-2}(X_2) = \cdots \\ &= w_n(X_{n-1}) - w_{-n}, \end{aligned} \tag{4}$$

where the w's are defined as

$$\begin{aligned} w_1 &= k_1(A)(B) \\ w_{-1} &= k_{-1}(C) \\ w_2 &= k_2(D) \\ &\cdots\cdots\cdots \\ w_n &= k_n(L) \\ w_{-n} &= k_{-n}(M)(N). \end{aligned}$$

The solution of this set of n equations is obtainable by determinants and may be put in the form

$$\left.\begin{aligned} \frac{1}{V_+} &= \frac{1}{w_1} + \frac{w_{-1}}{w_1 w_2} + \frac{w_{-1}w_{-2}}{w_1 w_2 w_3} + \cdots + \frac{w_{-1}w_{-2}\cdots w_{-(n-1)}}{w_1 w_2 \cdots w_n} \\ \frac{1}{V_-} &= \frac{1}{w_{-n}} + \frac{w_n}{w_{-n}w_{-(n-1)}} + \cdots + \frac{w_n w_{n-1}\cdots w_2}{w_{-n}w_{-(n-1)}\cdots w_{-1}} \\ V &= V_+ - V_-. \end{aligned}\right\} \tag{5}$$

If the over-all system is irreversible, $w_{-n} \equiv 0$, the term V_- vanishes. In our particular case this assumption has been made and is equivalent to the assertion that fibrin is not converted to fibrinogen. In view of the fact that fibrin is insoluble, this assertion is justified. The expression for V then takes the form

$$V = \frac{w_1 w_2 \cdots w_n}{w_2 w_3 \cdots w_n + w_{-1}w_3 \cdots w_n + w_{-1}w_{-2}w_4 \cdots w_n + \cdots + w_{-1}w_{-2}\cdots w_{-(n-1)}} \tag{6}$$

It will be noted that there are some special difficulties in the application of the steady state rate equation to the coagulation system, namely, that the thromboplastin — Ca^{++} complex (Th') is regenerated in the third reaction of equation (1) and that thrombin, although partially bound as the complex, $(T \cdot F)$, would be expected to accumulate as the over-all reaction proceeds. The first difficulty is eliminated by making the assumption that the concentration of Th' is given by the equilibrium value. The assumption is readily justified on the basis of the previously mentioned affinity of thrombo-

plastin for Ca^{++}. As regards the accumulation of thrombin, recent work of J. Ferry et al (1947) leads to the conclusion that the enzyme T is "carried down" with the clot. They have followed the time course of recoverable fibrinogen and such clot properties as opacity (associated with molecular weight), rigidity (associated with degree of cross linkage), tensile strength, etc. Their data show that the formation of a clot, which is taken as the end point in the determination of clotting times, occurs at a relatively early stage when ~ 10 per cent of the fibrinogen has been converted to fibrin. *After* clot formation has occurred, reaction in the clot continues as judged by the criteria mentioned above. The succeeding changes in opacity and rigidity show that even after all of the protein has been bound to the network (clot) the reaction proceeds to form additional cross linkages and more opaque structures. If the reactions which occur in the clot are due to the enzyme, thrombin, which is the only logical assumption, then these findings justify the portrayal of the last step as shown in equation (1) and the assumption that the subsequent reactions which occur *in* the clot, with the ultimate restitution of free thrombin to the system, are slow relative to the rate at which the clot is formed.

Under the foregoing assumptions, the expression for V in our particular case becomes

$$V = \frac{K_1 (Ca^{++})\,(P)\,(Th)\,(F)}{K_2 (P)\,(F) + K_3 (F) + K_4 (Th)\,(Ca^{++})}, \tag{7}$$

where the K's involve only the individual rate constants of the system. This equation gives the rate of production of fibrin as a function of the concentration of all components of the system. The next requirement is to obtain a relation explicit in time and in the concentration terms. Of particular interest is the relation between the "prothrombin time" and the concentration of prothrombin. Integrating equation (7) and solving for the time we obtain

$$\left.\begin{aligned} t_a &= \frac{1}{K_b} + \frac{K_a}{K_b} \cdot \frac{1}{(P)} \\ K_a &= \frac{K_3}{K_2} + \frac{K_4}{K_2} \frac{(Th)\,(Ca^{++})}{(F)} \\ K_b &= \frac{K_1}{K_2} \frac{(Ca^{++})\,(Th)}{a}. \end{aligned}\right\} \tag{8}$$

The above integration was carried out between the limits $t = 0$ and $t = t_a$, where t_a is the time required for the amount of fibrin produced

to reach a (t_a is commonly referred to as the prothrombin time). Further, the assumption was made that the steady state rate is constant, i.e., that the concentration of each component is constant during the time required for clotting and that $a = vt$. It is known that at the time of clot formation $a/(F_0) \sim .1$, where (F_0) is the initial concentration of fibrinogen and that (F) is not strictly constant. If this change is taken into account, we have $\frac{d(F)}{dt} = v$ and integrating between $(F) = (F_0)$ at $t = 0$ and $(F) = (F_0) - a$ at $t = t_a$, the result is that given in equation (8) except that K_a is now given by

$$K_a = \frac{K_3}{K_2} + \frac{K_4}{K_1 a}(Ca^{++})(Th) \log \frac{(F_0)}{(F_0) - a},$$

from which it is seen that if $a/(F_0)$ is small,

$$\log \frac{(F_0)}{(F_0) - a} = -\log [1 - a/(F_0)] \sim a/(F_0),$$

and K_a reduces to that given in equation (8). In equation (8) the value of a is simply neglected relative to (F_0); it is also necessary to neglect the amount of prothrombin converted to thrombin from $t = 0$ to $t = t_a$. Thus a is the amount of fibrin required to produce the clot or end point. Manifestly this quantity, and hence t_a, will vary with conditions which determine the properties of fibrinogen such as rigidity, tensile strength, etc.

From the equation relating t_a and (P), it is expected that the plot of t_a as a function of (P) will be a rectangular hyperbola with asymptotes parallel to the coordinate axes. It is thus seen that as (P) approaches zero, t_a increases without limit. As (P) is made increasingly large, the slope

$$\frac{dt_a}{d(P)} = -\frac{K_a}{K_b}\frac{1}{(P)^2}$$

approaches zero and t_a approaches a minimum limiting value given by $1/K_b$. Observe here a point to be discussed later, viz., that from equation (8) the limiting minimum value of t_a is inversely proportional to the concentration of thromboplastin and directly proportional to the amount of fibrin, a, which must be present at the end point. These results are certainly in general agreement with the characteristic shape of experimental curves, and the limits of t_a are compatible with physical concepts. In order to compare the equation with experiment, we take advantage of the fact that if t_a be plotted against $1/(P)$, the result should be a straight line of slope, K_a/K_b,

and ordinate intercept, $1/K_b$. A linear plot is also obtainable by plotting $t_a(P)$ against (P). It is of interest to compare both types of plot, since *graphically* the $1/(P)$ line tends to group the high (P) values while the (P) line gives equally spaced values of (P) equal weight. In view of the manner in which *Th* is involved in the constants, K_a and K_b, it should be found that lines from data obtained with higher levels of thromboplastin exhibit smaller slopes and intercepts.

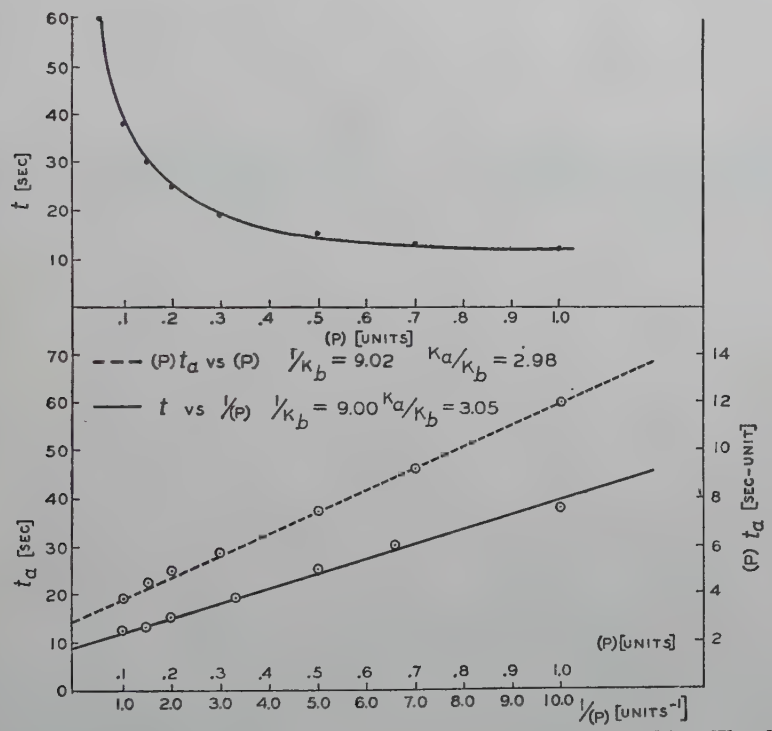

FIGURE 1. The unit of (P) is 100 per cent normal prothrombin. The dimensions of K_b and K_a/K_b are sec^{-1} and sec unit respectively.

Figure 1 shows data from A. Quick (see Kracke and Parker, 1940) from which it is seen that the foregoing remarks regarding the general shape of the curve are valid; also shown are the two linear plots of these same data. The agreement here may be regarded as quite satisfactory. Figure 2, from the paper of M. Hurn et al (1945), displays data obtained with two different thromboplastin preparations, all other conditions being identical. Figures 3 and 4 show the linear plots of these data. It is clear that the higher level of *Th* (Thromboplastin "D") gives rise to the line of smaller slope and in-

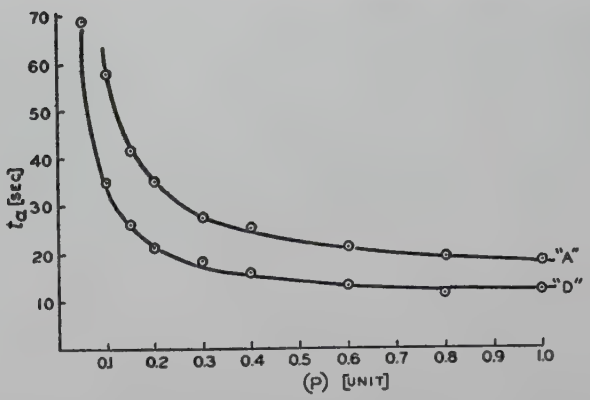

FIGURE 2. Data obtained with the thromboplastin "A" and "D" of Hurn et al (1945). Units as in Fig. 1. (One point, $t = 118$, $(P) = .05$ has been omitted from the "A" curve.)

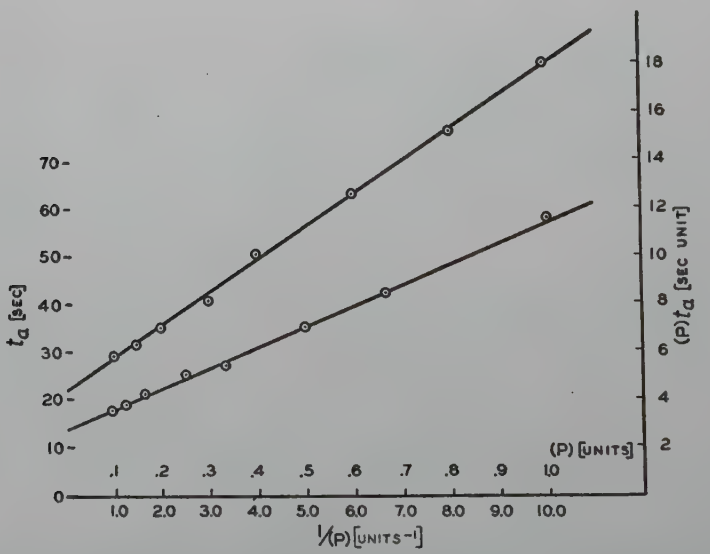

FIGURE 3. Linear plots of data from "A" curve Fig. 2. Upper curve is $(P)t_a$ vs. (P), $1/K_b = 13.7$ sec, $K_a/K_b = 4.30$ sec unit. Lower curve is t_a vs. $1/(P)$ $1/K_b = 13.4$ sec, $K_a/K_b = 4.31$ sec unit.

tercept as predicted. In view of the discussion to follow, it is of interest to point out that preparation "D" of M. Hurn et al was a commercial product designed to give Quick's normal t_a of 12 sec and that the parameters from Figures 2 and 4 check rather closely. Finally, Figure 5 shows the fits of the experimental points to the theoretical

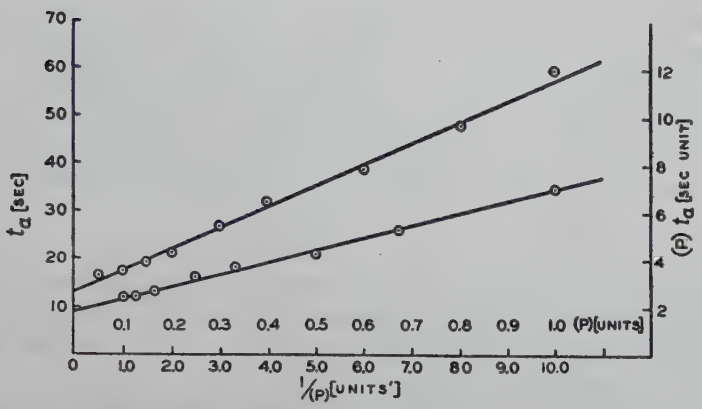

FIGURE 4. Linear plots of data from "D" curve Fig. 2. Upper line is $(P)t_a$ vs. (P), $1/K_b = 8.95$ sec, $K_a/K_b = 2.65$ sec unit. Lower curve is t_a vs. $1/(P)$, $1/K_b = 9.00$ sec, $K_a/K_b = 2.60$ sec unit.

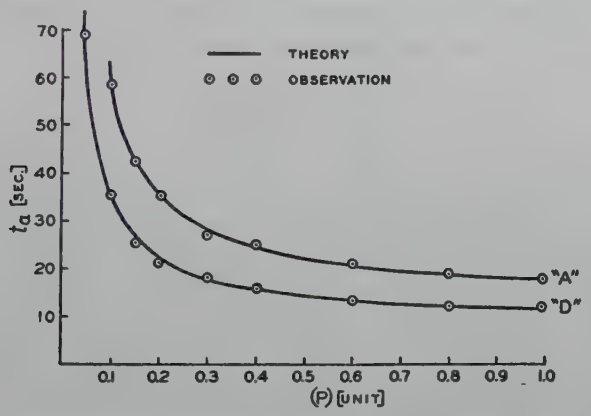

FIGURE 5. Computed theoretical curves. "A": $1/K_b = 13.6$ sec, $K_a/K_b = 4.31$ sec unit (mean values from Fig. 3). "D": $1/K_b = 8.98$ sec, $K_a/K_b = 2.63$ sec unit (mean values from Fig. 4).

hyperbola computed from the parameters, K_a and K_b, of the linear plot.

While these comparisons are apparently satisfactory in all cases and qualitatively the variation of the parameters K_a and K_b with (Th) has been correctly predicted, no data are available in which the value of (Th) was varied in a definite manner and data then obtained from which K_a and K_b could be determined. The values of K_b, other things being equal, should be proportional to (Th), as previously noted. Preliminary experiments designed to test this point have been carried out by the author and satisfactory agreement ob-

tained (Hearon, 1944, unpublished). It should be mentioned, however, that wide variations in (Th) cannot be tested due to the influence of changes in ionic strength and possibly due to the presence of inhibitors in the cruder preparations. In this sense the aforementioned work is not yet entirely satisfactory. However, the value of K_b is extremely useful and sufficiently accurate for comparing the potency of various thromboplastin preparations.

When prothrombin times are determined on prothrombin deficient plasmas, the actual result obtained clearly depends upon the activity of the thromboplastin preparation employed. It is usual, for this reason, to employ preparation of similar or identical activity or, alternatively, to seek some means of interpreting the results in terms of those which would have been obtained with a preparation with which the clinician is already familiar (See Hurn et al, 1940). As has been seen the value of $1/K_b$ may be obtained for any given preparation, directly from the t_a vs. $1/(P)$ graph. The ratio of two values obtained with different preparations is an index to the relative activities of the two preparations for, from equation (8)

$$\frac{K_{b1}}{K_{b2}} = \frac{(Th)_1}{(Th)_2},$$

where K_{b1} and K_{b2} are respectively the values of K_b for preparations one and two and $(Th)_1$ and $(Th)_2$ the corresponding thromboplastin concentrations. This ratio gives a convenient *numerical* basis for comparing thromboplastic activity. Also, if a given value of t_a is obtained with a thromboplastin preparation for which $1/K_b$ and K_a/K_b are known, the values which would have been obtained with any other preparation, for which $1/K_b$ and K_a/K_b are known, may be readily computed from the expression relating to t_a and (P).

Evidently there are many points which may now be discussed with some degree of precision in terms of the relation derived here. At this point only one or two will be mentioned. The general tendency has been, in arranging the concentration of the various components of the test system for prothrombin determination, to employ a great excess of all components except prothrombin in order that this may be the so-called "limiting factor" of the rate process. In principle this is sound, but it is practical only within limits. The distinct disadvantage of a great excess of thromboplastin is readily perceived from the equations presented. It has been seen that the clotting time approaches a minimum value, $1/K_b$, which is determined by the level of thromboplastin. In fact, with the usual experimental set-up, clotting times in the normal range already approach the limiting time

rather closely and in the range 70–100 per cent normal (P), differ only by 3–5 seconds from the minimum possible time and the clotting time is virtually independent of (P). The logical manner in which to avoid the difficulty is obviously not to further increase (Th), but to decrease (P), decrease (Th), or both.

This is most readily seen from the expression

$$t_a - 1/K_b = \frac{K_a}{K_b}\frac{1}{(P)},$$

which gives the difference between the observed time, t_a, and the minimum limiting time, $1/K_b$. The value of K_a/K_b decreases with increasing (Th). Therefore, the limiting value, $1/K_b$, is more closely approached for a given value of (P) the higher the value of (Th), and is eventually reached experimentally at lower values of (P) when higher values of (Th) are employed.

Along similar lines are the following considerations: It is evident from the experimental curves as well as the analytical expression that the slope of the t_a vs. (P) curve,

$$\frac{dt_a}{d(P)} = -\frac{K_a}{K_b}\frac{1}{(P)^2},$$

decreases with increasing (P) and that the slope at any (P) decreases with increasing (Th). In regions of small slope, a given change in (P) is reflected as a relatively small change in t_a. We may ask what variation in (P) may be detected if t_a may be determined within prescribed limits. The answer clearly depends upon the level of (P) in question and the parameters, K_a and K_b. The matter is made precise as follows: Let us agree that two groups of determinations of t_a are *significantly* different if their means differ by Δt† and impose the condition that this time variation shall correspond to a given variation in (P), say $\Delta(P)$. The ratio of these two quantities must satisfy the expression for the slope of the t_a vs. (P) curve of the system employed. The required value of (P) follows at once and is seen to depend on the value of K_a/K_b,

$$(P)^* = \left[\frac{K_b}{K_a}\left|\frac{\Delta(P)}{\Delta t}\right|\right]^{\frac{1}{2}}, \qquad (9)$$

where $(P)^*$ is the required value of (P). Stated otherwise, having the value of K_b/K_a we determine the value of (P) at or below which we must operate in order that a difference in t_a, which we must ac-

†In general Δt will be $3\sqrt{2}\sigma$ where σ is the standard deviation of the sets of determinations.

cept, reflect a difference in (P) which we have agreed to accept. Experimentally, it is then necessary to dilute the plasma being investigated to the point where $(P) \leqq (P)^*$. Also the loss in sensitivity which accompanies the use of too high (Th) at a given level of (P) is clear from equation (9).

In summary, it may be said that the treatment given here of the kinetics of the reactions occurring in the coagulation process gives a basis to many empirical procedures already adapted and points out ways of improving such procedures. Certain procedures found useful clinically and previously carried out empirically, e.g., adjusting various thromboplastin preparations to the potency of a given one, determining the relation between the times obtained with two preparations, etc., are greatly aided by the availability of the analytical expression, or they may be done completely analytically. The bearing of this discussion on *in vivo* clotting is not readily assessed at this point. Certainly, however, the majority of the information available to date on the coagulation process was derived from systems of the type covered here.

The author is much indebted to Dr. M. F. Morales for valuable criticism and discussion.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 10, 1948

A NOTE ON THE UNITS OF MEMBRANE PERMEABILITY TO WATER

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In the usual experimental technique, the membrane permeability to water in the units of cm/sec is not measured directly. The quantity which is usually obtained may be considered to be a measure of a coefficient of penetrability having the dimensions time/length. The purpose of this paper is to show that by introducing the bulk modulus of water, an expression is obtained from which it is possible to calculate the water permeability in the units of cm/sec from the values in conventional units.

The membrane permeability, h_S, of a substance, S, is defined as the mass flowing across the surface per unit time, per unit area, and per unit concentration gradient. The dimensions of h_S are thus length divided by time. This is not directly measured in the case of water. It is the purpose here to obtain a method of estimating the permeability of water, h_w, analogous to that for any other substance. What is directly measurable is the flow rate of water per unit area per unit pressure difference. If p_e and p_i are the external and internal pressures in dynes/cm acting on a membrane of area A, then the inward rate of flow of water, Q_w in cm^3/sec, will be given by (Rashevsky and Landahl, 1940)*

$$Q_w = \xi A (p_e - p_i), \tag{1}$$

where ξ is a coefficient for the given membrane which has the units sec/cm. One might refer to ξ as the coefficient of penetrability of water since its units are not the same as those of permeability. The conventional laboratory units for "water permeability," are $\mu^3/\mu^2/$min/atmosphere pressure difference ($\mu \equiv$ micron, Lucké, 1940). Since the density of water is almost unity, the numerical value is unchanged if μ^3 is replaced by micro-micrograms, though the dimensions are changed. If this change is made, the conventional values become measures of ξ. We shall write ξ^* for the value expressed in laboratory units, although strictly μ^3 should be replaced by micro-micrograms.

* Attention is here drawn to an error in the units of ξ in this reference, the dimensions of ξ being time/length or sec/cm instead of cm sec as given there.

Then the "water permeability" in the above units, ξ^*, can be converted to ξ in sec/cm from the relation

$$\xi\,(\text{cm}^{-1}\,\text{sec/cm}) = 1.67 \times 10^{-12}\,\xi^*\,(\mu^3/\mu^2/\text{min/atm}). \tag{2}$$

If we consider the pressure difference across the membrane as being due only to the solute concentration difference, $c_i - c_e$ in gms/cm^3, then if M is the molecular weight of the solute, T the absolute temperature and $R = 8.3 \times 10^7$ is the gas constant,

$$p_e - p_i = \frac{RT}{M}\,(c_i - c_e)\,, \tag{3}$$

so that

$$Q_w = RT\,\xi\,A\,(c_i - c_e)/M\,. \tag{4}$$

The quantity $RT\,\xi/M$ has the units of permeability (cm/sec), but the concentration difference refers to the solute.

The expression which defines h_w is given by

$$Q_w = h_w\,A\,(c_{we} - c_{wi})\,, \tag{5}$$

where c_{we} and c_{wi} are the external and internal concentrations of water in grams per cubic centimeter.

Consider the flow Q_w as being due to a pressure difference $(p_e - p_i) = \Delta p$ which results in a difference in the concentration of water. If a pressure Δp is applied to a mass m_w of water of volume V, there is a change in volume $-\Delta V$ given by

$$\Delta V = -\,V\Delta p/M_B\,, \tag{6}$$

where $M_B = 2.07 \times 10^{10}$ dynes/cm^2 is the bulk modulus for water at 20° C and at one atmosphere. If ρ_w is the actual density of water for a given set of conditions,

$$\rho_w V = \text{constant}\,, \tag{7}$$

and therefore

$$\Delta\,\rho_w/\rho_w = -\,\Delta V/V. \tag{8}$$

Hence we have

$$\Delta\,p = \Delta\,\rho_w\,M_B/\rho_w \doteq \Delta\,\rho_w\,M_B\,, \tag{9}$$

since $\rho_w \approx 1$.

In the absence of a solute $\Delta\rho_w \equiv \Delta c_w$. But in the presence of the solute this is not correct. However, the component of Δc_w which is given by $\Delta\rho_w$ in the general case is just the change in concentration of water which is effective in producing a transport of water.

Thus we shall substitute $(p_e - p_i) = \Delta p$ by $M_B \Delta c_w = M_B (c_{we} - c_{wi})$ from equation (9) into equation (1) and obtain

$$Q_w = \xi M_B A (c_{we} - c_{wi}). \tag{10}$$

Comparing equations (10) and (5) we then obtain

$$h_w = M_B \xi / \rho_w = M_B \xi \text{ cm/sec}. \tag{11}$$

Thus if ξ^* is the value of the penetrability in $\mu^3/\mu^2/\text{min/atm}$, h_w can be obtained from $1.67 \times 10^{-12} \times 2.07 \times 10^{10}\ \xi^*$ or

$$h_w = 0.034\ \xi^* \text{ cm/sec}, \tag{12}$$

if we assume that the compressibility is still about the same in the presence of solutes.

If both solvent and solute were dilute solutions, then $\Delta c_w / M_w$ would equal $\Delta c / M$. Then converting ξ^* in $\mu^3/\mu^2/\text{min/atm}$ to $(RT\xi/M)^*$ moles water/μ^2/min/moles solute per liter would also give the permeability h_w^* in moles/μ^2/min/moles per liter which has the dimensions of length/time. Since water is not a dilute solution, we must take this into account to obtain h_w^* by multiplying $(RT\xi/M)^*$ by fifteen, the ratio of compressibility $(1/M_B)$ of water to that compressibility water would have if it behaved as a perfect gas at unit density. The value of h in cm/sec can be obtained from h_w^* by multiplying h_w^* by 1.67×10^9. This is equivalent to the result obtained above.

For a number of echinoderm eggs the values for h_w calculated from equation (12) using data by B. Lucké (1940) lie in the range 3×10^{-3} to 14×10^{-3} cm/sec while erythrocytes of ox and man have values of h_w about 0.1 cm/sec. The value of 3 or 4×10^{-3} cm/sec for *Arbacia* eggs may be compared with the values of the permeability of *Arbacia* eggs to some other substances. For ethylene glycol and glycerol the values of the permeability are 6×10^{-6} cm/sec and 8×10^{-7} cm/sec (Jacobs and Stewart, 1932). The permeability to oxygen has been estimated as being greater than or of the order of magnitude of 2×10^{-4} cm/sec (Rashevsky, 1940, p. 24).

The author is indebted to Dr. J. Z. Hearon for reading and discussing this manuscript.

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 10, 1948

ON THE THEORY OF BLOOD-TISSUE EXCHANGE OF INERT GASES: VI.

VALIDITY OF APPROXIMATE UPTAKE EXPRESSIONS

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It is shown that the equation of inert gas uptake by a distinct parallel tissue-blood arrangement coincides, under certain conditions, with two formulations which neglect the possible existence of a blood-tissue barrier. The first of these approximations is the classic von Schrötter equation in continuous form, whereas the second is the empirical one frequently used by contemporary authors. The condition for coincidence is that the product of permeability and blood-tissue exchange surface greatly exceed the rate of blood flow to the tissue. It is difficult to examine this condition at present because of a dearth of gas permeability measurements and because apparently there exist no measurements of surface and flow on the same tissue. A compilation is made of such values as are available, and it is found that on the assumption that gas permeabilities are of the order of 1×10^{-3} cm sec^{-1}, the conditions for neglecting the blood-tissue barrier may be met in many cases and certainly not met in many others. It is concluded that under these circumstances the more exact equations, taking into account the barrier, should be employed, at least until precise independent measurements justifying the approximations become available.

In a series of papers appearing during recent years, the present authors (1944a, 1944b, 1944c, 1945a, 1945b; hereinafter referred to as I, II, III, IV, and V, respectively) have endeavored to formulate a quantitative theory of inert metabolite uptake, taking into account all factors which in the light of present knowledge seem of first-order importance. No attempt has been made, however, to relate this development to more limited expressions, derived by other authors, in particular, to the early and classic one of H. von Schrötter (1906). It seems necessary to clarify the relationship at this time because at least some contemporary workers have regarded their von Schrötter-like expressions as conceptually different from ours. To anticipate the results of this paper, we shall say that in a "distinct parallel" system (IV), when the product of permeability and surface is much greater than the blood flow through a tissue, then the limiting form of our equation is essentially identical with the von Schrötter expression. This is a straightforward mathematical fact. Whether or not

this limiting condition is actually attained in real systems is a distinct question, and one which only experimental measurement can answer. In the authors' opinion, existing data are inadequate for the decision, although experiments now in progress* seem very promising.

There are possibly three fundamentally different arrangements of tissues with respect to the circulation (IV); of these, it will presently be obvious that the von Schrötter treatment is applicable only to one, namely, what we have called "distinct parallel". It is, therefore, the simplest case of this arrangement which we shall choose in order to demonstrate the relationship between the two mathematical descriptions. In the original von Schrötter treatment the possible difference in solvent power between the blood and tissues was neglected, but this is a matter easily corrected by dividing the tissue volume by a partition coefficient, α, which for inert gases is one or less than one.

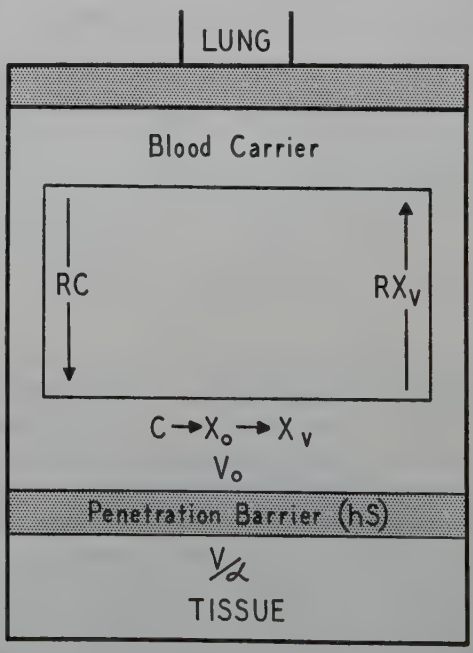

FIGURE 1. Model of a simple exchange system in which transport is via the vascular flow between the point of solute supply (e.g., the lung) and that of exchange (e.g., a tissue region of volume V and homogeneous with respect to its solution properties). In the von Schrötter case the barrier penetration factor hS is neglected.

* Experiments by Dr. Falconer Smith and his associates, aimed at the measurement of h for radioactive inert gases (plasma membrane of myxomycetes), are currently being conducted at the National Institute of Health.

We shall treat, as usual, the uptake of an inert metabolite at some localized region in the circulation, assuming that all blood leaving this region is charged with metabolite at a constant concentration, C. The problem will be to find the amount, ϕ, of this metabolite within a distant tissue region which is in diffusion contact with the blood (Figure 1). Let us denote by V_0 the volume of blood which flows through the tissue region in question during one circulation time, and by V the volume of the tissue. After the manner of von Schrötter (*loc. cit.*), we may now think of the transfer problem in the following approximate way: V_0 cm^3 of blood pick up V_0C gm of metabolite at the uptake region, and this amount is distributed *instantaneously* between blood and remaining tissue in proportion to their volumes, i.e., a fraction $V_0/(V_0 + V/\alpha)$, remains in the blood and a fraction, $(V/\alpha)/(V_0 + V/\alpha)$ is allotted the tissue. The V_0 cm^3 of blood now return to the uptake region and become re-saturated, the net amount picked up at this time being just equal to that which it gave up to the tissue. The cycle is then repeated. It is easy to see that the amount of metabolite in the tissue after n cycles is,

$$\phi(n) = V_0C\left\{\left(\frac{V/\alpha}{V_0 + V/\alpha}\right) + \left(\frac{V/\alpha}{V_0 + V/\alpha}\right)^2 + \cdots + \left(\frac{V/\alpha}{V_0 + V/\alpha}\right)^n\right\} = \frac{VC}{\alpha}\left\{1 - \left(\frac{V/\alpha}{V_0 + V/\alpha}\right)^n\right\}. \tag{1}$$

Expression (1) is essentially von Schrötter's final result. For comparison with our equations, however, a slight transformation is desirable. If we think in terms of an equivalent *continuous* circulation rate, R cm^3 sec^{-1}, through the tissue, it is clear that the volume of blood which has passed up to the time t is Rt; since V_0 cm^3 is the volume which passes per cycle, the number of cycles up to the time t is,

$$n = \frac{R}{V_0}t. \tag{2}$$

Using (2), we may re-write (1) as

$$\phi(t) = \frac{VC}{\alpha}(1 - e^{kt}); \tag{3}$$

$$k = -\frac{R}{V_0}\log_e\left(1 + \frac{\alpha V_0}{V}\right). \tag{4}$$

This same system may be treated more accurately by the simultaneous solution of two differential equation (I, IV). We shall de-

note the permeability of the blood-tissue barrier by h, and the exchange surface by S; x_0 will be the *average* metabolite concentration along the capillaries, x, the average in the tissue, and x_v, the concentration of metabolite in the blood leaving the tissue region. Now x_0, of course, will lie between C and x_v, its exact value depending on the instantaneous concentration gradient along the capillary. We shall take into account the existence of this gradient only phenomenologically, by assuming that over the course of the absorption,

$$x_0 = C - f(C - x_v)\,; \quad f, \text{ constant.} \tag{5}$$

Employing expression (5), the arterio-venous accumulation term, $R(C - x_v)$, becomes $(R/f)(C - x_0)$. In all past papers we have taken $f = 1$, whence the coefficient of $(C - x_0)$ was to be interpreted as the rate of blood flow. It is clear that if other values of f are chosen, the original equations and solutions still hold, provided the "R" is reinterpreted as $1/f$ times the true rate of blood flow. For example, if x_0 is to be the arithmetic mean of C and x_v, then $f = 1/2$, and R/f is twice the rate of blood flow.

It is not difficult in certain restricted cases to set up the partial differential equations for this system and so to deduce the axial concentration gradient theoretically. For example, if z measures distance along a capillary axis, ρ measures the radial distance from the capillary axis, $C_B(z, t)$ is the concentration of solute in the capillary, $C_T(\rho, z, t)$ is the concentration of solute in the (assumed) homogeneous tissue, D_T, the diffusion coefficient in the tissue, and ρ_0 is the radius of the capillary, then the governing equations are:

$$\pi\rho_0^2 \frac{\partial C_B}{\partial t} = R\frac{\partial C_B}{\partial z} - 2\pi\rho_0 h(C_B - C_T)\,,$$

$$D_T \nabla^2 C_T = \frac{\partial C_T}{\partial t}\,,$$

with the boundary condition that, $-D_T(\partial C_T/\partial\rho)_{\rho=\rho_0} = h[C_B - C_T(\rho_0)]$, and that C_T remains finite as $\rho \to \infty$. The advantage gained by attempting an exact solution of these equations may, nevertheless, be illusory, because there are available virtually no good measurements of the physical constants involved, and the detailed capillary geometry is much more complicated than this model suggests.

Adopting (5) we may write the differential equations of the system as,

$$V_0 \frac{dx_0}{dt} = \frac{R}{f}(C - x_0) - hS(x_0 - \alpha x)\,; \tag{6}$$

$$V\frac{dx}{dt} = hS(x_0 - \alpha x). \tag{7}$$

The solution of equation (6) and (7) is (I),

$$\phi_0(t) = V_0 x_0 = V_0 C\left\{1 + \frac{k_2 + \frac{2R}{V_0 f}}{k_1 - k_2} e^{k_1 t} - \frac{k_1 + \frac{2R}{V_0 f}}{k_1 - k_2} e^{k_2 t}\right\}; \tag{8}$$

$$\phi(t) = Vx = \frac{V}{\alpha} C\left\{1 + \frac{k_2}{k_1 - k_2} e^{k_1 t} - \frac{k_1}{k_1 - k_2} e^{k_2 t}\right\}; \tag{9}$$

where,

$$k = -\frac{\frac{R}{V_0 f} + \frac{hS}{V_0}\left(1 + \frac{\alpha V_0}{V}\right)}{2} \pm 1/2\left\{\left[\frac{R}{V_0 f} + \frac{hS}{V_0}\left(1 + \frac{\alpha V_0}{V}\right)\right]^2 - 4\frac{RhS}{fV_0 V}\right\}^{1/2}. \tag{10}$$

The plus or the minus sign before the second term of equation (10) corresponds arbitrarily, to k_1 and k_2. A comparison of (3) with (9) readily suggests that the physical assumptions which justify the von Schrötter expression, (3), are those which would cause one of the two exponentials in (9) to disappear. This reduction to one exponential could be effected by having $k_1 = k_2$; however, it can be shown that this equality would require certain terms in (10) to assume complex values, which requirement would be physical nonsense. The second, and only plausible, method is to have one of the two absolute values of k, say k_1, be much larger than the other, whereupon (9) becomes,

$$\phi(t) \cong \frac{V}{\alpha} C(1 - e^{k_2 t}). \tag{11}$$

For $|k_1| >> |k_2|$, it is apparent from (10) that,

$$\left[\frac{R}{V_0 f} + \frac{hS}{V_0}\left(1 + \frac{\alpha V_0}{V}\right)\right]^2 >> 4\frac{\alpha RhS}{fV_0 V}. \tag{12}$$

The structure of condition (12) suggests that it can be achieved either when $R/f >> hS$ or $R/f << hS$. To show this more clearly, we shall adopt the following notation: $R/f = X$; $hS = Y$; $(\alpha V_0/V) = r$; and

in the event that $X >> Y$, the small quantity $Y/X = \varepsilon$; in the converse case, $X << Y$, we have the small quantity, $X/Y = \eta$. We may then write from (10),

$$k_2(X >> Y) = -\frac{1}{2V_0}\left\{ X + Y(1+r) - X\left[1 + 2(1-r)\varepsilon + (1+r)^2\varepsilon^2 \right]^{1/2} \right\}; \tag{13}$$

$$k_2(X << Y) = -\frac{1}{2V_0}\left\{ X + Y(1+r) - Y(1+r)\left[1 + \frac{2(1-r)}{(1+r)^2}\eta + \frac{1}{(1+r)^2}\eta^2 \right]^{1/2} \right\}. \tag{14}$$

It can be stated on experimental grounds that we need not be concerned with values of $r > 1$. It will be noted that the special case, $r = 1$, is a critical one in both (13) and (14), but one which need not concern us here. When $r < 1$, it will be obvious to the reader from an inspection of expressions (13) and (14) exactly what numerical conditions are being assumed in retaining only the linear terms (in ε or η) in the binomial theorem expansion of the radical, yielding,

$$k_2 = -\frac{\alpha hS}{V}, \tag{15}$$

when $R/f >> hS$, and

$$k_2 = -\frac{R}{V_0}\cdot\frac{1}{2f}\left[1 - \frac{1-r}{(1+r)^2} \right]; \text{ when } R/f << hS. \tag{16}$$

It is clear that (3) can be regarded as an approximation identical with (11) provided that we can show (4) to be essentially the same as (16). Exact coincidence cannot be expected because of the approximations already made. Nonetheless, it may be shown graphically (Fig. 2) as well as by expansion in a MacLaurin series that for $0 \leqq r \leqq 0.6$, the coefficient of $-R/V_0$ in (16) is not appreciably different from $\log_e(1 + r)$. The identity of (4) and (16) is thus reasonably complete for this range of r if we assume, as in the past, that the average axial concentration gradient is such as to make $f \cong 1$. To summarize, then, if in the differential equations for a distinct parallel system, (8), (9), it be assumed that, (a) there exists along the absorbing blood vessel a concentration gradient of the type $f \cong 1$, (b) $hS >> R$ (in such a way as to justify the expansion of

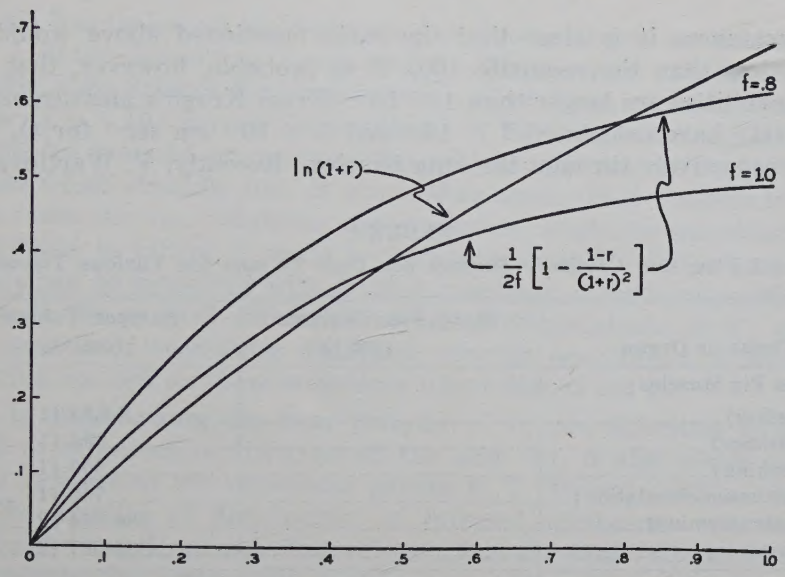

FIGURE 2. Graph to show approximate coincidence of the single exponent as derived in the von Schrötter theory ($1n(1+r)$) and in the limiting case of the differential equation method. The coincidence in the physiologically important range $0 < r < .6$ is seen to depend on f (see text), being best when $f = 1$, and increasingly poor as f decreases from unity.

the radical in (14)), and (c) $0 \leqq \alpha V_0/V \leqq 0.6$, then the uptake as a function of the time is given by von Schrötter's expression (3), (4).

In the absence of suitable experimental values of h, we can only speculate about the plausibility of the condition, $R/f << hS$. Let us divide this inequality by V_T, the tissue volume, and assume that $f = 1$. We may then fairly require that

$$\left[\frac{\frac{S}{V_T}}{\frac{R}{V_T}}\right] \quad h \text{ exceed at least 100 to justify (11) and (16).}$$

We have not found in the existing literature simultaneous measurements of blood flow and surface-volume ratios on any tissue. However, it may be seen from the data gathered in Table 1 that the ratio in question may be expected to lie between the two extremes, 277 h and 460,000 h. The decision regarding the validity of the von Schrötter type of approximation is thus seen to depend on accurate values of the permeability of the plasma membrane to gases. Such values are not abundant. In early rough calculations we, as well as others, have assumed values of the order of 1×10^{-5} cm sec^{-1}. Under these

circumstances it is clear that the ratio mentioned above would be much less than the requisite 100. It is probable, however, that the permeabilities are larger than 1×10^{-5}. From Krogh's measurements we (III) have calculated 7×10^{-3} and 3×10^{-4} cm sec^{-1} for O_2 and CO_2 respectively through the lung barrier. Recently, V. Wartiovaara

TABLE 1

Blood Flow and Capillary Surface per Unit Volume for Various Tissues

Tissue or Organ	Blood Flow/Volume (sec^{-1})	Surface/Volume (cm^{-1})
Guinea Pig Muscles:		
(resting)		3,8,32 (1)
(massage)		200 (1)
(working)		390 (1)
(maximum circulation)		750 (1)
(gastrocnemius)		186-254 (2)
(masseter)		304-507 (2)
Mouse Muscle:		
gastrocnemius		486-640 (2)
masseter		726-923 (2)
Guinea Pig Fat:		
Fat fat tissue		23.5 (3)
Lean fat tissue		64.1 (3)
Frog Muscle		190 (1)
Horse Muscle		240 (1)
Dog Muscle		590 (1)
Thyroid	.0933 (4)	
Kidney	.025 (4)	
Liver	.025, .006, .017 (4)	
Brain	.023 (4)	
Intestines	.012 (4)	
Spleen	.007 (4)	
Stomach	.004 (4)	
Hand	.0022 (4)	

The numbers in parenthesis refer to authorship of data:

(1) Krogh (1936)
(2) Sjöstrand (1937)
(3) Gersh and Still (1945)
(4) Best and Taylor (1943)

(1944) has measured the permeability of *tolypellopsis* for deuterium, and I. Holm-Jensen, A. Krogh and V. Wartiovaara (1944) that of certain plant tissues for various ions; all of these values are of the order of 1×10^{-3} cm sec^{-1}. Accepting 1×10^{-3} as a round number for h, we see that the extremes of the critical ratio are .277 and 460 — values which straddle 100. It would thus appear that whereas in certain cases the von Schrötter approximation might be quantitatively justifiable, in others it would be very poor indeed. Until tissue constants can be measured with greater precision, a preference must be given to the general differential equation formulations (I–V) which are capable of describing situations wherein penetration is strongly limiting, *as well as those situations where this is not so.*

In emphasizing the clear priority of H. von Schrötter with regard to equations of the type of (3) and (4), it also seems opportune to mention the important papers of T. Teorell (1937a, 1937b) on the kinetics of distribution of injected substances. So far as we are aware, Professor Teorell's work is the first rational attempt to describe the whole-body distribution process by means of an approximate system of differential equations. It is regretted that this paper had not come to our attention at the time the present work was begun.

This paper was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of The University of Chicago.

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